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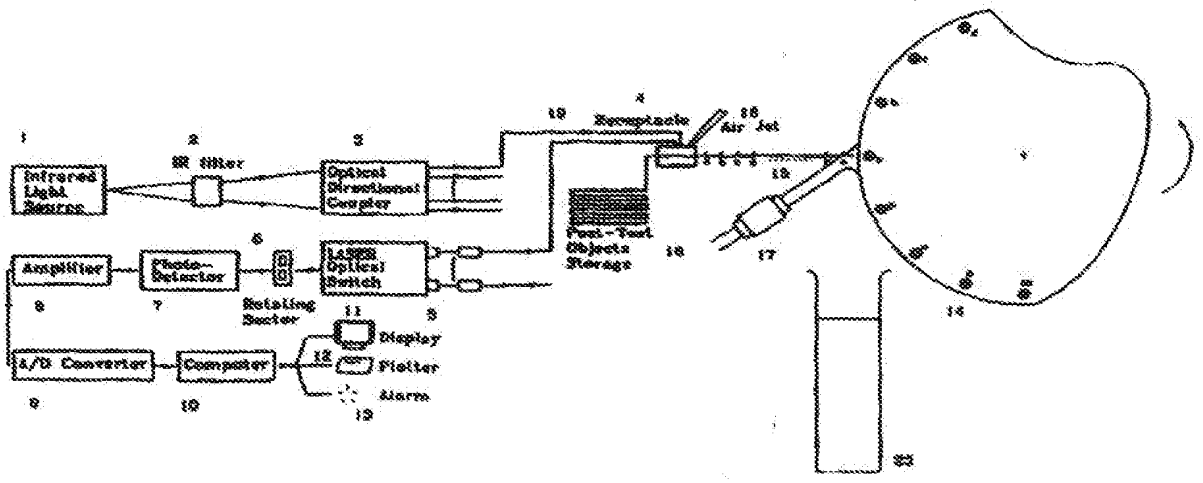

(57) Abstract

An automatic non-destructive real time infrared system includes a special bundle of fiber optics having the ability to convey infrared light waves to solid organic-base compounds and receive reflected infrared light waves from the same. A sample of a manufactured solid compound or organic-base is conveyed by mechanical and pneumatic means (15, 18) to a holding receptacle (4) located under the field of view of the fiber optics probe (19). The probe (19) is directly linked to a spectrophotometer to obtain a spectrum. The spectrophotometer is linked to a computer system (10) determining the exact dissolution measurement of each manufactured solid organic-base compound. The compacted solid of organic-base compound is released from the receptacle (4) by an ejection means (18) to be dispensed in a holding container (23) for storage. The storage container (23) maintains the sample sequence. A new sample is dispensed to the holding receptacle (4) allowing for new measurement of dissolution.

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NON-DESTRUCTIVE IDENTIFICATION OF TABLET AND TABLET DISSOLUTION BY MEANS OF INFRARED SPECTROSCOPY ANALYSIS

Background of Invention

The present invention is directed to an infrared spectrophotometer system. Such systems have utility in various fields, including the application of dissolution through hardness measurements, such as in pharmaceutical industry. It is desirable that such a system should be adaptable to mass production techniques so that tablets and solid organic-base compounds could be analyzed at high speed. It would also be desirable if such a system could effectively operate without the need for complicated chemical analysis and complicated chemometeric tools. Ideally such a system should incorporate safety mechanisms to automatically turn off the production system when an unsafe condition is detected. Additionally, such a system should have the capability of sensing errors in the system, such as missing compound, missing potency, or excessive presence of compound occur.

Summary of Invention

An object of this invention is to provide an automatic non-destructive near infrared spectroscopic measurement of dissolution which fulfills the above needs.

A further object of this invention is to provide such a system which has a particular utility for tablet dissolution, such as used in the pharmaceutical industry.

In accordance with this invention, the automatic near infrared spectroscopy system for measuring tablet dissolution through hardness includes a probe, with fiber optics bundle, connected to a near infrared spectrophotometer analyzing energy passing through the fiber optics bundle directed at the resting tablet in the holding receptacle. A

plurality of pre-coated tablets departing their forming cavities fall into a holding drum. A sample tablet departing its cavity is conveyed to the receptacle instead of falling into the holding drum via a diverting mechanism which is activated periodically. The presence of the pre-coated tablet in the receptacle shuts off the diverting mechanism preventing any tablet to be conveyed to the receptacle. When the pre-coated tablet is secured in the receptacle a beam of near infrared light waves is energized, passed through the fiber optics bundle, and reflected back to the same fiber optics bundle to be passed again to the spectrophotometer for a certain period of time during which a tablet spectrum is generated. The tested pre-coated tablets are automatically removed from the receptacle in a way allowing them to be stored in the proper sequence to correspond with their acquired data.

In a preferred practice of the invention, the testing of the pre-coated tablets, departing from the supply station, is synchronized with their perspective forming cavities. The system preferably also includes a feedback signal generated by the computer to stop the tableting supply station when the dissolution measurement reaches an unacceptable value. The system preferably also includes an air ejection mechanism to remove the pre-coated tablets from the receptacle once the dissolution test is completed, allowing it to be stored in the proper sequence corresponding with the acquired data.

Sensors may be located suitably positioned for determining various conditions, such as the presence and absence of the tablets in the receptacle, correspondence of tablets with their forming cavities, and correspondence of the spectrum of tablet dissolution with each tablet and its cavity.

The Drawing

Figure 1 is a representative view of an automatic non-destructive near infrared spectroscopic machine in accordance with this invention;

Figure 2a is a top plan view of a portion of the system shown in figure 1 during actuation of the diversion of the tablet from the supply station to the tablet delivery mechanism leading to the receptacle of the infrared fiber optics sensor;

Figure 2b is a top plan view of a portion of the system shown in figure 1 during deactuation away from the supply station which permits the tablets to fall into a holding drum;

Figure 3 is a top plan view of a portion of the system in figure 1 depicting the tablet conveying mechanism to the receptacle of the infrared fiber optics sensor which leads to post-test objects storage;

Figure 4 is a partly sectional side view of the system shown in figure 1 depicting the receptacle holding one end of the infrared fiber optics sensor aimed at a tablet to be tested;

Figure 5 shows the near infrared absorption spectrum for a tablet, of a certain product, with known hardness of 0.8 kp;

Figure 6 shows superimposed near infrared absorption spectra for two tablets of known hardness of 0.8kp and 2.0kp of the said product in figure 5;

Figure 7 shows superimposed near infrared absorption spectra for three tablets of known hardness of 0.8kp, 2.0kp, and 4.0kp of the said product in figure 5;

Figure 8 shows superimposed near infrared absorption spectra of four tablets of known hardness of 0.8kp, 2.0kp, 4.0kp, and 6.0kp of the said product in figure 5;

Figure 9 shows superimposed near infrared absorption spectra of five tablets of known hardness of 0.8kp, 2.0kp, 4.0kp, 6.0kp, and 8.0kp of the said product in figure 5;

Figure 10 shows superimposed near infrared absorption spectra of six tablets of known hardness of 0.8kp, 2.0kp, 4.0kp, 6.0kp, 8.0kp, and 10.0kp of the said product in figure 5;

Figure 11 shows the linear correlation between the integrated near infrared absorbency of each of the six tablets in figure 10 and their nominal hardness;

Figure 12 shows a stack of superimposed near infrared absorption spectra of a set of four tablets, of known hardness ranging from 5.0kp to 6.0kp, of a certain product different from the said product in figure 5;

Figure 13 shows a stack of superimposed near infrared absorption spectra of a set of four tablets, of known hardness ranging from 8.0kp to 9.0kp, of the said product in figure 12;

Figure 14 shows a stack of superimposed near infrared absorption spectra of a set of four tablets, of known hardness ranging from 11.0kp to 12.0kp, of the said product in figure 12;

Figure 15 shows a stack of superimposed near infrared absorption spectra of a set of four tablets, of known hardness ranging from 14.0kp to 15.0kp, of said product in figure 12;

Figure 16 shows a superimposed stack of the near infrared absorption spectra of each set of tablets in figures 12, 13, 14, and 15;

Figure 17 shows the linear correlation between the integrated near infrared absorbency of each of the four sets of tablets in figure 16 and their nominal hardness;

Detailed Description

The present invention is directed to an automatic non-destructive infrared system which is capable of determining dissolution in mass production operation by measuring the hardness of organic-base objects. Such measurements could be applied to any solid organic-base compound and have a particular utility for being applied to solids such as tablets used in the pharmaceutical industry. The general operation of the system is illustrated in figure 1. As shown therein, the system includes a supply of station 14 which is made of a continuous indexing machine of tablet pressing cavities a, b, c, d, ..., p made of any suitable shape such as round, spherical, triangular, diamond, rectangular, square, hexagonal, etc.. Each indexing machine may contain in excess of 356 cavities. From the supply station 14 tablets normally fall into holding reservoir 23. From the supply station 14 samples of pressed tablets are directed by actuator 17, when energized, to conveyor 15 to be automatically detached from conveyor 15 to receptacle 4 through air jet 18. From the supply station 14 actuator 17 is intermittently activated to direct each sample tablet to conveyor 15 maintaining the exact departing sequence of figure 2a. Actuator 17 is retracted when samples are not needed and the actual production is directed to holding drum 23 of figure 2b.

Conveyor 15 delivers each sample tablet assisted by the air jet 18 to lower parts 21 of receptacle 4, which is automatically opened to contain one tablet sample at a time as in figure 3. The infrared fiber optics sensor 19 is firmly attached to upper plate 20 of receptacle 4 in figure 4. Infrared fiber optics sensor 19 is aimed at the sample tablet 22 inside receptacle 4, which is supported by lower parts 21. Tablet 22 inside receptacle 4 is spectrophotoscopically analyzed during a certain

period of time to measure dissolution and obtain specific identity. When completed, the lower parts 21 of receptacle 4 are automatically opened and the air jet 18 again directs the tested sample 22 to enter the post-test objects storage station 16, maintaining the same sequence maintained during the departure from the supply station 14.

The sample tablet 22 in receptacle 4 receives pulsated near infrared light waves through infrared fiber optics sensor 19 which receives its generated waves from optical directional coupler 3. Optical directional coupler 3 contains multiple coupled channels feeding infrared light waves through several cables of infrared fiber optics to permit sequential analyses of multiple sample tablets. The Optical directional coupler 3 receives its pulsated near infrared light waves through infrared filter 2.

The near infrared filter 2 filters light wave lengths, permitting only near infrared light waves to flow to the optical directional coupler 3. The infrared light source 1 is a halogen lamp generating light wave lengths which are directed to the infrared filter 2.

The fiber optics infrared cable 19 contains two branches permitting near infrared light waves to travel from one of its branches to sample tablet 22 in receptacle 4, while the other branch of the near infrared fiber optics cable 19 carries reflected light waves from sample tablet 22 in receptacle 4 to LASER optical switch 5, creating interference effect by separating the incoming beam into two parts, then introducing a path difference and finally recombining the beam, generating specific time recording of interferometric pulsated light waves ranging from 700nm to 2450nm infrared spectra.

The rotating sector 6 synchronizes reflected interferometric pulsated light waves of the same wave lengths of the same spectrum

of both the sample tablet 22 and a comparative standard object selected prior to test procedure. The rotating sector 6 directs the synchronized reflected interferometric pulsated light waves to the photo-detector 7. The resulting beam intensity recorded as a function of optical path difference with infrared sensitive detector is called an interferogram.

The photo-detector 7 measures the reflected intensity of near infrared light waves of sample tablet 22. The photo-detector 7, in the same manner, has previously measured the reflected intensity of near infrared light waves for the known standard object for comparison to sample tablets prior to sending the sample tablets a, b, c, d, ..., p to receptacle 4.

The intensity of the near infrared light waves aimed at each tablet sample 22 through the sending branch of the fiber optics cable 19, entering receptacle 4, is greater than the intensity of the near infrared light waves of the fiber optics cable branch 19 exiting receptacle 4 by the amount of infrared light waves absorbed by the sample tablet 22.

The said photo-detector 7 measures intensity of near infrared light waves in analog form and sends the measurements to amplifier 8.

The amplifier 8 proportionally amplifies the received analog measurements sent by photo-detector 7. The amplifier 8 sends the proportionally amplified measurements to the analog/digital converter 9.

The analog/digital converter 9 converts the proportionally measured analog measurements into corresponding proportionally digital measurements suitable for computer 10.

Computer 10 computing the Fourier transformation of the interferogram yields the infrared spectrum. Computer 10

mathematically divides the known measurements of the standard object by each measurement of the sample tablets 22. The said computer 10 records the data in its resident memory and applies Fourier transformation analysis of the relative reflectance or absorbency of every sample tablet as compared to the known standard object to obtain the near infrared spectrum for each tablet. The near infrared spectra generated by computer 10 are displayed on display monitor 11, and plotted on an electromechanical plotter 12.

Alarm 13 is automatically energized to cause the supply station 14 to take an instantaneous corrective action.

A significant part of this invention is the mathematical integrations of the absorbency values found for each sample tablet 22 extended throughout the entire span of each spectrum achieved at computer 10. This mathematical integration is equivalent to the area of each spectrum for each sample tablet 22. The area also can be used as a functional measure of the energy absorbed by sample tablet 22. The outcome is therefore a single value representing a distinctive measure of sample tablet hardness. Since hardness is the measure dissolution, it is evident that measuring hardness is measuring also dissolution. The details of illustrating the integrated area for each spectrum are best shown in figures 5-10 and figures 12-15. This integration permits the system figure 1 to obtain a single value of hardness (dissolution) for each tested sample tablet as a measure of the ability of the supply station 14 to produce products with desired hardness (dissolution).

The integration permits the supply station 14 to take corrective action of tablet production instantaneously, whereas the current industry method of measuring hardness (dissolution) may provide the supply station with an indication of its status within a few hours, leading to the

destruction of tablets produced if the hardness (dissolution) is unacceptable.

An additional significant part of this invention showed in figure 11 and figure 16 is the discovery of the straight line correlation between the corresponding integrated area of each tablet spectrum and its actual hardness (dissolution). This discovery provides predictive data of the behavior of organic-base objects that are made of the same chemical compounds and produced under the same conditions to interpolate and extrapolate the necessary data for practical applications.

A further feature of this invention is the critical ability to discriminate between similar products, including their chemical contents and the dosages of the essential elements required to produce the product. Additionally, the tablet can be interrogated to obtain accurate data of the presence or absence of foreign objects important to the safety of the public.

Advantageously, system figure 1 operates without the need for time consuming chemical analyses or destruction of sample tablets to measure hardness (dissolution). In practice, the integrated value of each spectrum of each sample tablet is displayed on computer display 11, indicating the hardness (dissolution) value which must be within acceptable upper and lower tolerance control limits which are also displayed on computer display 11.

In the illustrated embodiment, sample tablet 22 is shown as a round-shaped object. Other shapes of organic-base objects may be used whereupon the lower parts of receptacle 4 are adapted to contain the sample object shapes.

In the illustrated embodiment, receptacle 4 is illustrated as an automatic container that is opened at a specific instant to accommodate sample tablet 22, whereupon sample tablet 22 may be placed on a transporting mechanism to be passed directly under the field of view of cable 19.

A further feature of system figure 1 is the inclusion of alarm devices 13 disposed at suitable locations for the sensing of the rate of increase of sample tablet hardness to an unacceptable level. The alarm devices may be directly interlocked with the supply station 14.

The invention may be practiced with various modifications. For example, figure 3 illustrates an arrangement wherein a single sample tablet 22 is situated in receptacle 4. Multiple sample tablets can be situated and arranged in a suitable receptacle. Additionally, supply station 14 can direct the produced objects to be placed under multiple cables to test all objects produced without the necessity of receptacle 4.

It is to be understood that the above description is intended to exemplify the practice of the invention and may be varied without departing from the concepts of the invention. For example, the invention has been described wherein each sample tablet is disposed to its appropriate location at receptacle 4 assisted by air jet 18. Other manners of conveying the sample tablet may also be used including a miniature robotic mechanism. Also, the post-test objects storage may be replaced by a multiple disc mechanism wherein each disc contains many cavities. Each disc is loaded automatically by a miniature robot. Once all cavities of each disc are filled, the disc is dropped downward, allowing a fresh disc containing multiple cavities to replace the filled one. Similarly, the actuator 17 may be replaced by a robotic

mechanism to load tablet samples from supply station 14 to receptacle 4, and unload tested sample tablets from receptacle 4 to post-test objects storage 18. The upper plate 20 of said receptacle 4 is either fixed as tablet objects are conveyed to receptacle 4 or movable as tablet objects are not conveyed to said receptacle 4. The lower parts 21 of the receptacle 4 can be removed to facilitate conveying the upper plate 20 carrying the fiber optics cable 19 to the field of view of the tablet objects.

What is Claimed is:

1. An automatic non-destructive near infrared system comprising a continuous supply of organic-base tablet objects loaded on a conveyor via an actuator mechanism maintaining the sequence of said tablets on the said conveyor, a receptacle comprising of an upper plate holding bundle of fiber optics cable or plurality of fiber optics cables receiving infrared light waves from opto-directional coupler, conveying near infrared light waves, said receptacle comprising also a pair of lower parts accommodating presence of objects, an air jet device assisting in directing the objects to rest at said receptacle and depart from said receptacle, said tablets departing from receptacle are arranged in post-test objects storage maintaining their original sequence, said bundle of fiber optics cable or plurality of fiber optics cables carrying dual layers of fiber optics of upstream cable layers feeding infrared waves and downstream cable layers conveying reflected infrared waves to LASER optical switch, a means of conveying and amplifying data received from said downstream fiber optics cable or plurality of cables to said infrared spectrophotometer to computer, said computer computes mathematical integration in an output form for each spectrum generated by said spectrophotometer, said output form is conveyed by electronic means to a computer display monitor displaying the status of said tablet objects in Fourier transformation form, said computer output form is integrated and conveyed to a plotter comprising two directional motions responding to said computer output drafting the status of said spectrum, said computer output form is conveyed also to alarm sensor declaring the status of said tablet object, said alarm comprising sensorial information

conveyed to supply production machine of tablet objects; said computer integrated output form yields linear phenomena conveyed to said plotter and said computer display plots integrated absorbency in one direction and nominal hardness (dissolution) in the perpendicular direction.

2. The system of claim 1, wherein continuous supply of tablet objects loaded on a conveyor via an actuator mechanism electro-pneumatically actuated, and said actuator mechanism comprising electro-pneumatic solenoid actuating devices.

3. The system of claim 2, wherein said continuous supply of tablet objects loaded on a conveyor via an actuator mechanism is synchronized between each cavity and its corresponding tablet object placed onto conveyor.

4. The system of claim 3, wherein said conveyor is means to convey tablet objects maintaining their departing sequence by said actuator.

5. The system of claim 1, wherein said an air jet device assisting in directing the objects is an electro-pneumatic device comprising electro-pneumatic solenoid device actuated in a manner to maintain the same sequence of tablet objects.

6. The system of claim 1, wherein said receptacle comprising an upper plate holding bundle of fiber optics cable or plurality of fiber optics cables, said receptacle upper plate is fixed where tablet objects are conveyed to said receptacle.

7. The system of claim 1, wherein said receptacle comprising of an upper plate holding a bundle of fiber optics cable or plurality of fiber optics cables, said receptacle upper plate is movable where tablet objects are not conveyed to said receptacle.

8. The system of claim 7, wherein said tablet objects are not conveyed to said receptacle resulting from multiple rows of tablet objects needing to be tested at real time speed.

9. The system of claim 1, wherein said pair of lower parts accommodating presence of objects is automatically actuated.

10. The system of claim 1, wherein said tablets departing from receptacle are arranged in a post-test objects storage maintaining their original sequence resulting in total control of every production lot by describing their recorded data at any given time serving public safety, security and ease of audit.

11. The system of claim 1, wherein said bundle of fiber optics cable or plurality of fiber optics cables carrying dual layers of fiber optics of upstream cable layers feeding infrared waves and downstream cable layers conveying reflected infrared waves, combine in a unified bundle at the point of entering said receptacle, while downstream cable layers separates after departing said receptacle.

12. The system of claim 11, wherein said downstream cable layers separates after departing said receptacle, said downstream cable branches into same plurality as entered into said receptacle to enter LASER optical switch.

13. The system of claim 1, wherein said means of conveying and amplifying data received from said downstream fiber optics cable or plurality of cables to said infrared spectrophotometer to computer, includes means of conducting multiple parallel processing of all spectra corresponding to tablet objects.

14. The system of claim 1, wherein said means of conveying and amplifying data received from said downstream fiber optics cable or plurality of cables to said infrared spectrophotometer to computer,

includes means of sequencing and storing data for sequential processing of all spectra corresponding to tablet objects.

15. The system of claim 1, wherein said computer computes mathematical integration in an output form for each spectrum generated by said spectrophotometer, resulting in a single value for each spectrum of the tablet object.

16. The system of claim 15, wherein said resulting single value for each spectrum of the tablet object is measured against two predetermined tolerance values, one representing an upper acceptable value and the other representing a lower acceptable value, determining the acceptability of the tablet hardness (dissolution).

17. The system of claim 1, wherein said output form is conveyed by electronic means to computer display monitor includes an electronic mechanism sequencing the data of each stored spectrum, arranging the hardness (dissolution) data in the proper sequence.

18. The system of claim 17, wherein said electronic means includes a video recording mechanism recording the status of sample tablets or the status of the entire production of tablets.

19. The system of claim 1, wherein said output form is conveyed by electronic means to a computer display monitor displaying the status of said tablet objects in Fourier transformation form, includes several other mathematical computations.

20. The system of claim 1, wherein said computer output form is integrated and conveyed to a plotter comprising two directional motions, and responding to said computer output, which drafts the status of said spectrum, said computer output form can be constructed in three dimensional axes describing the absorbency distribution and

said plotter is capable of plotting the three dimensional axes utilizing its two directional motions.

21. The system of claim 1, wherein said computer output form is conveyed also to alarm sensor declaring the status of said tablet object, said alarm comprising sensorial information, including audio, visual and electronic interlocking mechanisms, conveyed to the supply station to provide adequate warning and stop the supply station if warranted.

22. The system of claim 1, wherein said computer integrated output form yields linear phenomena conveyed to said plotter and said computer display of integrated absorbency in one direction and nominal hardness (dissolution) in the perpendicular direction yields to all mathematical formulae governing the behavior of linear equations.

23. The system of claim 22, in practice, provides predictive data of similar or dissimilar organic-base products vital to verification practices.

24. The system of claim 22, in practice identifies the presence or absence of the exact composition of each tablet substance.

25. The system of claim 24 in practice identifies the presence or absence of foreign substances in the composition of tablet compounds.

26. The system of claim 1, in combination therewith, provides unique signatures of organic-base tablet objects in any form proprietary to each product.

AMENDED CLAIMS

[received by the International Bureau on 12 March 1996 (12.03.96); original claims 8,10,12,19 and 22-26 cancelled; original claims 1,3-5, 18,20 and 21 amended; new claims 27-30 added; remaining claims unchanged (7 pages)]

1. An automatic non-destructive near infrared system comprising a continuous supply of tablets loaded on a conveyor via an actuator mechanism maintaining a sequence of said tablets on said conveyor, a receptacle comprising of an upper plate holding a bundle of at least one fiber optic cable receiving infrared light waves from an opto-directional coupler, conveying near infrared light waves, said receptacle further comprising a pair of lower parts accommodating presence of objects, an air jet means for directing the objects to rest at said receptacle and to depart from said receptacle, said tablets departing from receptacle are arranged in storage maintaining said sequence, said bundle of at least one fiber optic cable carrying upstream and downstream layers of fiber optics, said upstream cable layers feeding infrared waves and said downstream cable layers conveying reflected infrared waves to an optical switch means, a means for conveying and amplifying data received from said downstream cable layers to said infrared spectrophotometer to a computer, said computer computes mathematical integration in an output form for each spectrum generated by said spectrophotometer; said output form is conveyed by electronic means to a computer display monitor displaying status of said tablets in Fourier Transformation form, said computer output form is integrated and conveyed to a plotter comprising two directional motions responding to said computer output drafting the status of said spectrum, said computer output form is further conveyed to an alarm means declaring a status of said tablets, said alarm means comprising information conveyed to a supply means of tablets; said computer integrated output

form yields linear phenomena conveyed to said plotter and said computer display plots integrated absorbency in a first direction and nominal hardness (dissolution) of the tablets in a second direction perpendicular to said first direction.

2. The system of claim 1, wherein continuous supply of tablet objects loaded on a conveyor via an actuator mechanism electro-pneumatically actuated, and said actuator mechanism comprising electo-pneumatic solenoid actuating devices.

3. The system of claim 2, wherein said conveyor includes a plurality of cavities and wherein said continuous supply of tablets loaded on said conveyor via an actuator mechanism is synchronized between each of said plurality of cavities and its corresponding tablet placed onto conveyor.

4. The system of claim 3, wherein said conveyor maintains a departing sequence of said tablets from said actuator.

5. The system of claim 1, wherein said air jet means for directing the objects is an electro-pneumatic solenoid device actuated to maintain an orderly sequence of said tablets.

6. The system of claim 1, wherein said receptacle comprising an upper plate holding bundle of fiber optics cable or plurality of fiber optics cables, said

receptacle upper plate is fixed where tablet objects are conveyed to said receptacle.

7. The system of claim 1, wherein said receptacle comprising of an upper plate holding a bundle of fiber optics cable or plurality of fiber optics cables, said receptacle upper plate is movable where tablet objects are not conveyed to said receptacle.

8. Cancelled

9. The system of claim 1, wherein said pair of lower parts accommodating presence of objects is automatically actuated.

10. Cancelled

11. The system of claim 1, wherein said bundle of fiber optics cable or plurality of fiber optics cables carrying dual layers of fiber optics of upstream cable layers feeding infrared waves and downstream cable layers conveying reflected infrared waves, combine in a unified bundle at the point of entering said receptacle, while downstream cable layers separates after departing said receptacle.

12. Cancelled

13. The system of claim 1, wherein said means of conveying and amplifying data received from said downstream fiber optics cable or plurality of cables to said infrared spectrophotometer to computer, includes

means of conducting multiple parallel processing of all spectra corresponding to tablet objects.

14. The system of claim 1, wherein said means of conveying and amplifying data received from said downstream fiber optics cable or plurality of cables to said infrared spectrophotometer to computer, includes means of sequencing and storing data for sequential processing of all spectra corresponding to tablet objects.

15. The system of claim 1, wherein said computer computes mathematical integration in an output form for each spectrum generated by said spectrophotometer, resulting in a single value for each spectrum of the tablet object.

16. The system of claim 15, wherein said resulting single value for each spectrum of the tablet object is measured against two predetermined tolerance values, one representing an upper acceptable value and the other representing a lower acceptable value, determining the acceptability of the tablet hardness (dissolution).

17. The system of claim 1, wherein said output form is conveyed by electronic means to computer display monitor includes an electronic mechanism sequencing the data of each stored spectrum, arranging the hardness (dissolution) data in the proper sequence.

18. The system of claim 17, wherein said electronic means includes a video recording means.

19. Cancelled

20. The system of claim 1, wherein said computer output form is integrated and conveyed to a plotter which responsive to said computer drafts the status of said spectrum, said computer output form in a three dimensional illustrating an absorbency distribution.

21. The system of claim 1, wherein said alarm means includes means for stopping the supply station.

22. Cancelled

23. Cancelled

24. Cancelled

25. Cancelled

26. Cancelled

27. An apparatus comprising:

means for exposing a sample to a plurality of light beams of varying wavelengths thereby creating a plurality of reflected light beams;

means for measuring intensities of said plurality of reflected light beams and further generating a spectrum of relative reflectance or absorbance of said plurality of reflected light beams by the sample;

means for performing a Fourier transform on said spectrum; and

means for integrating said spectrum of relative reflectance or absorbance of said plurality of reflected light beams by the sample thereby determining hardness of the sample.

28. A method comprising the steps of:

exposing a sample to a plurality of light beams of varying wavelengths thereby creating a plurality of reflected light beams;

measuring intensities of said plurality of reflected light beams and further generating a spectrum of relative reflectance or absorbance of said plurality of reflected light beams by the sample;

performing a Fourier transform on said spectrum; and

integrating said spectrum of relative reflectance or absorbance of said plurality of reflected light beams by the sample thereby determining hardness of the sample.

29. An apparatus comprising:

means for exposing a sample to a plurality of light beams of varying wavelengths thereby creating a plurality of reflected light beams;

means for measuring intensities of said plurality of reflected light beams and further generating a spectrum of relative reflectance or absorbance of said plurality of reflected light beams by the sample;

means for performing a Fourier transform on said spectrum; and

means for integrating said spectrum of relative reflectance or absorbance of said plurality of reflected light beams by the sample thereby determining contents of the sample.

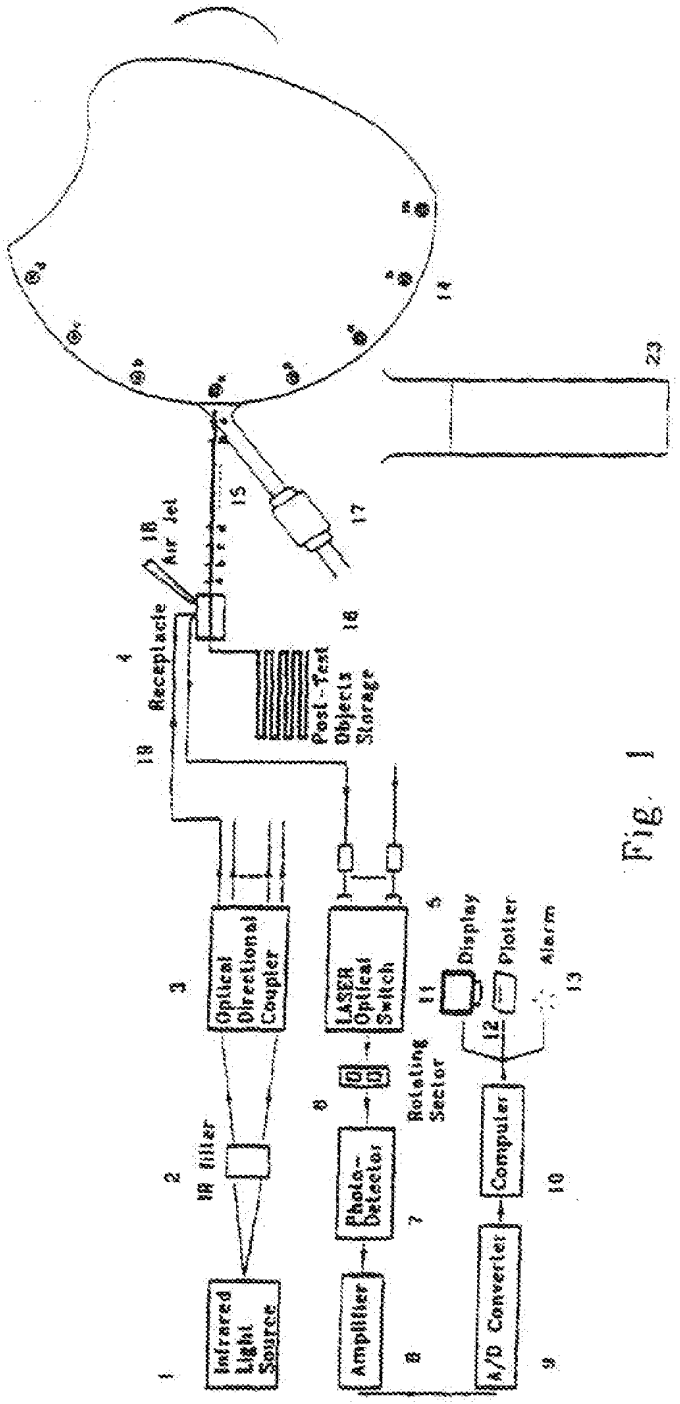
30. A method comprising the steps of:

exposing a sample to a plurality of light beams of varying wavelengths thereby creating a plurality of reflected light beams;

measuring intensities of said plurality of reflected light beams and further generating a spectrum of relati[illegible] reflectance or absorbance of said plurality of reflected light beams by the sample;

performing a Fourier transform on said spectrum; and

integrating said spectrum of relative reflectance or absorbance of said plurality of reflected light beams by the sample thereby determining contents of the sample.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LASER Optical Switch
Photo-Detector
Rotating Sector
Amplifier
A/D Converter
Computer
Display
Plotter
Alarm

Fig. 1

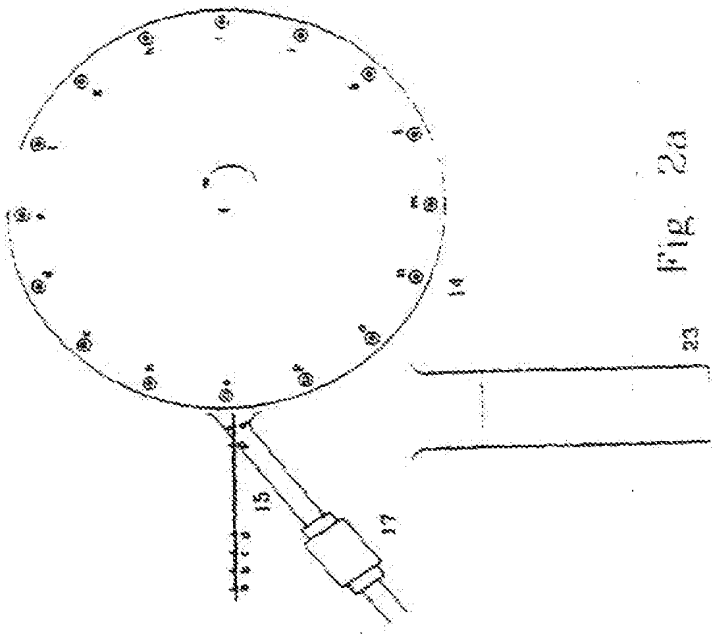


Fig. 2a

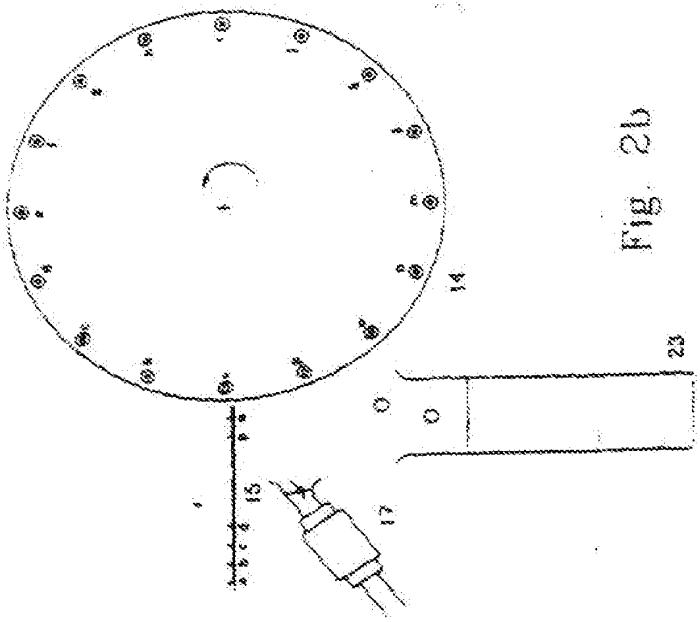


Fig. 2b

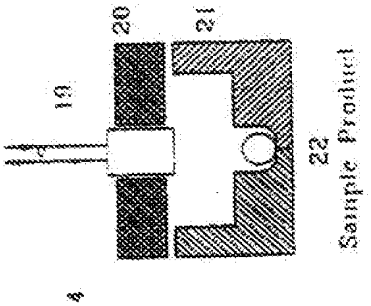

19
20
21
22
Sample Product
4

Fig. 4

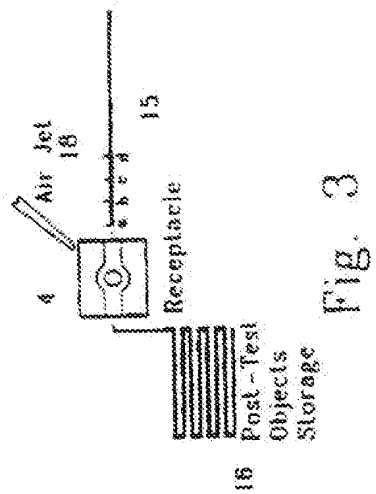

Air Jet
18
15
4
Receptacle
Post-Test
Objects
Storage
16

Fig. 3

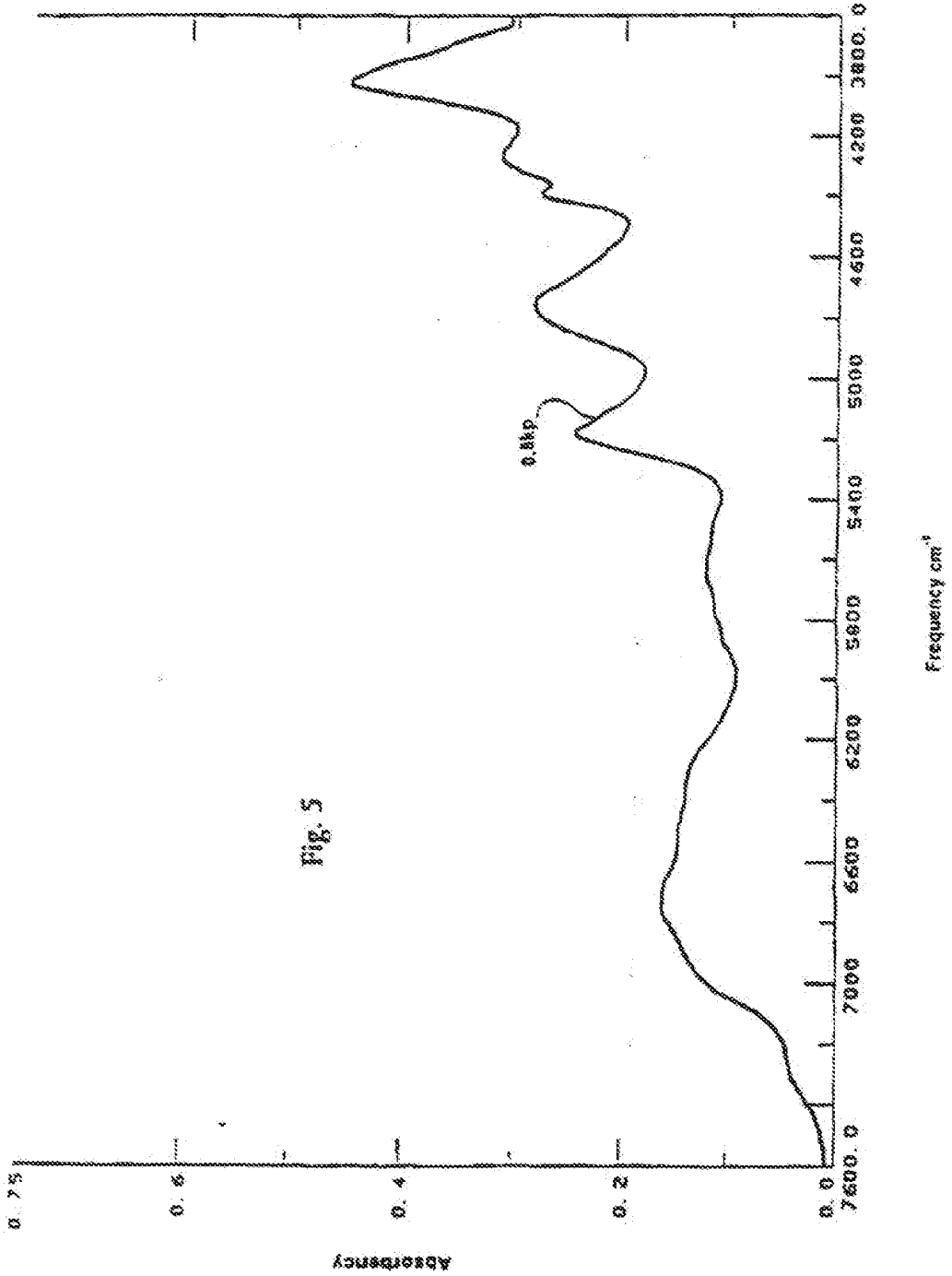
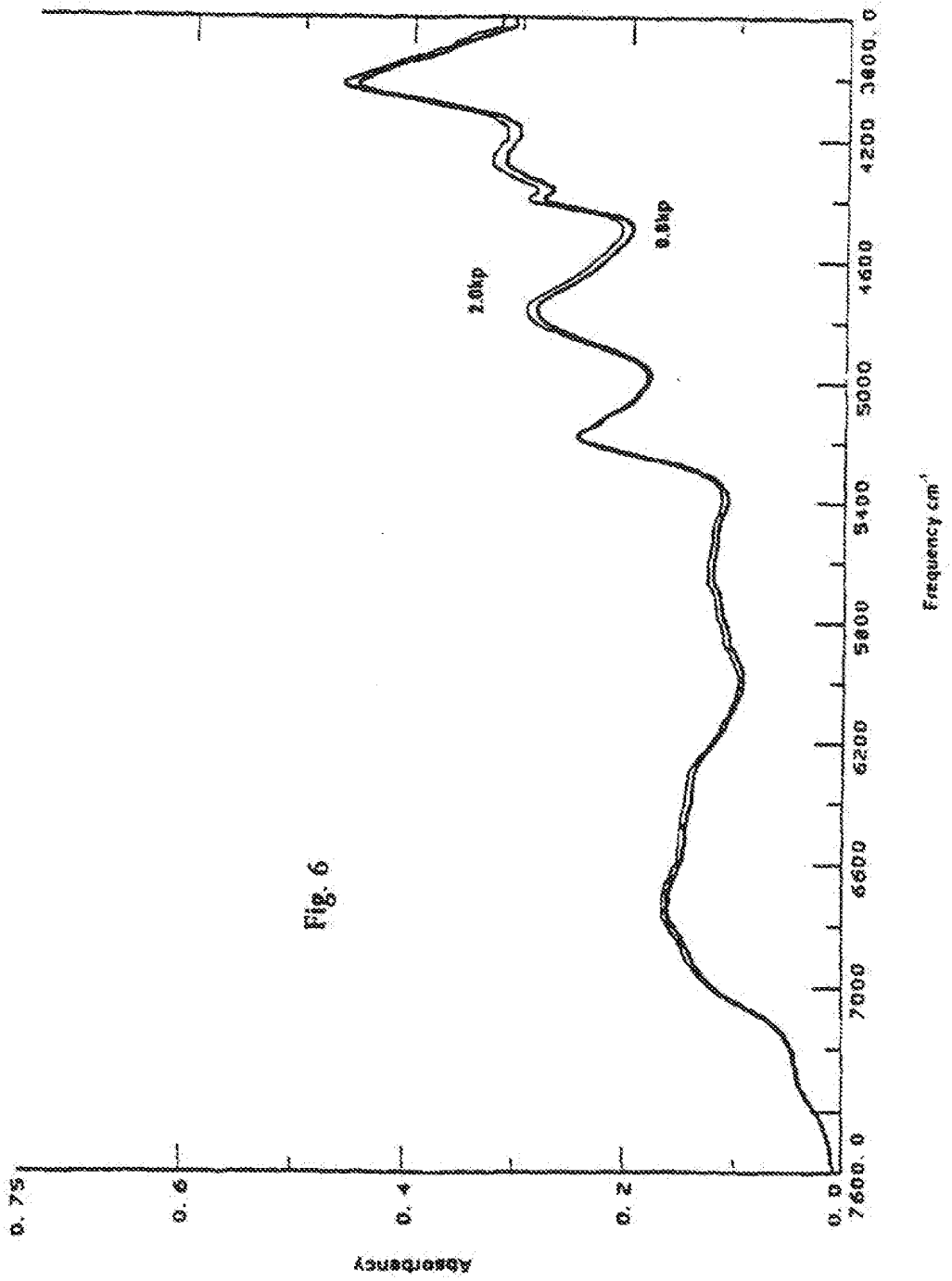

0.8kp
Absorbency
0.75
0.6
0.4
0.2
0.0
7600.0
7000
6600
6200
5800
5400
5000
4600
4200
3800.0
Frequency cm⁻¹

Fig. 5


Absorbency
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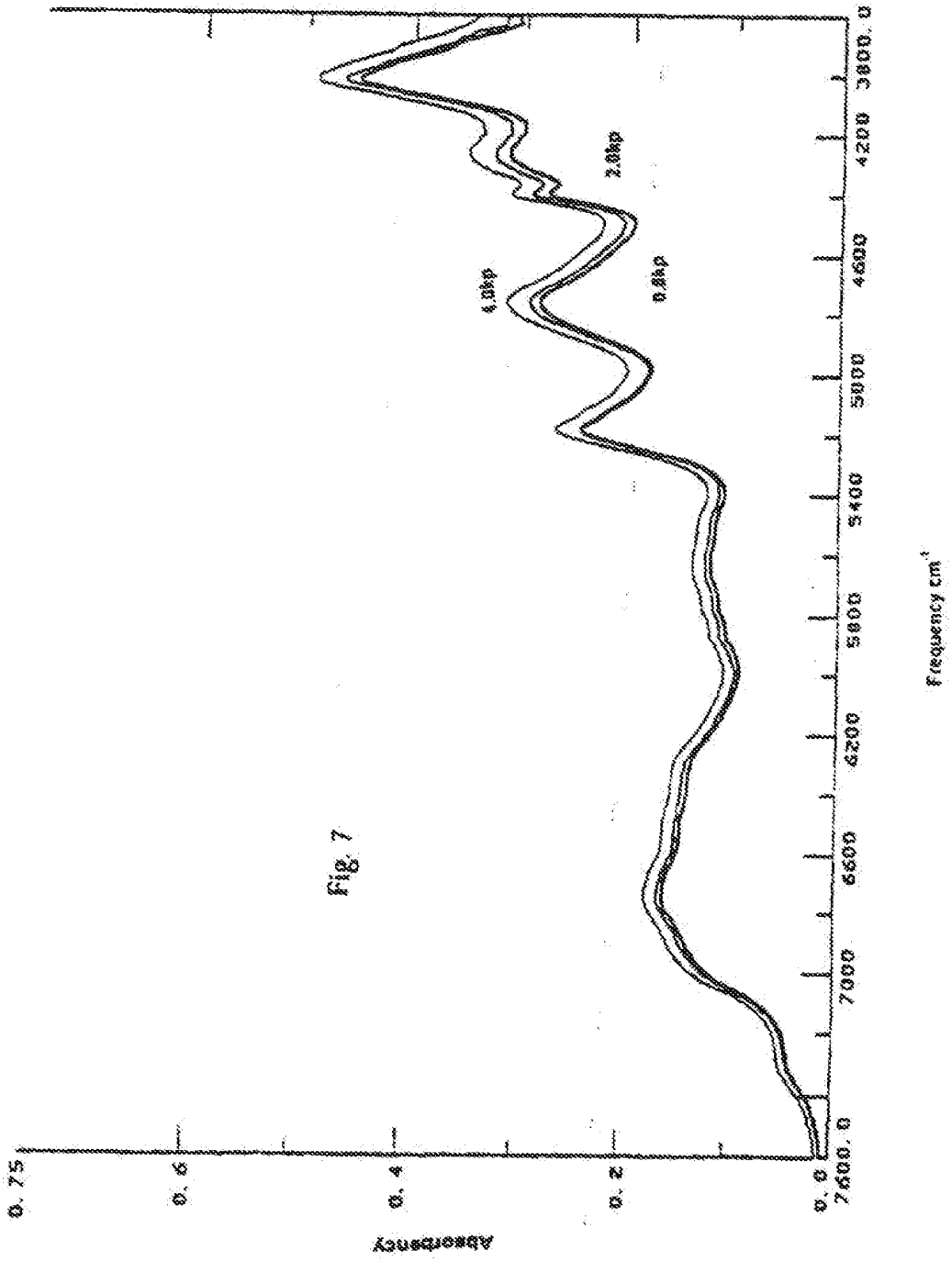
3800.0
Frequency cm⁻¹
2.0kp
0.8kp

Fig. 6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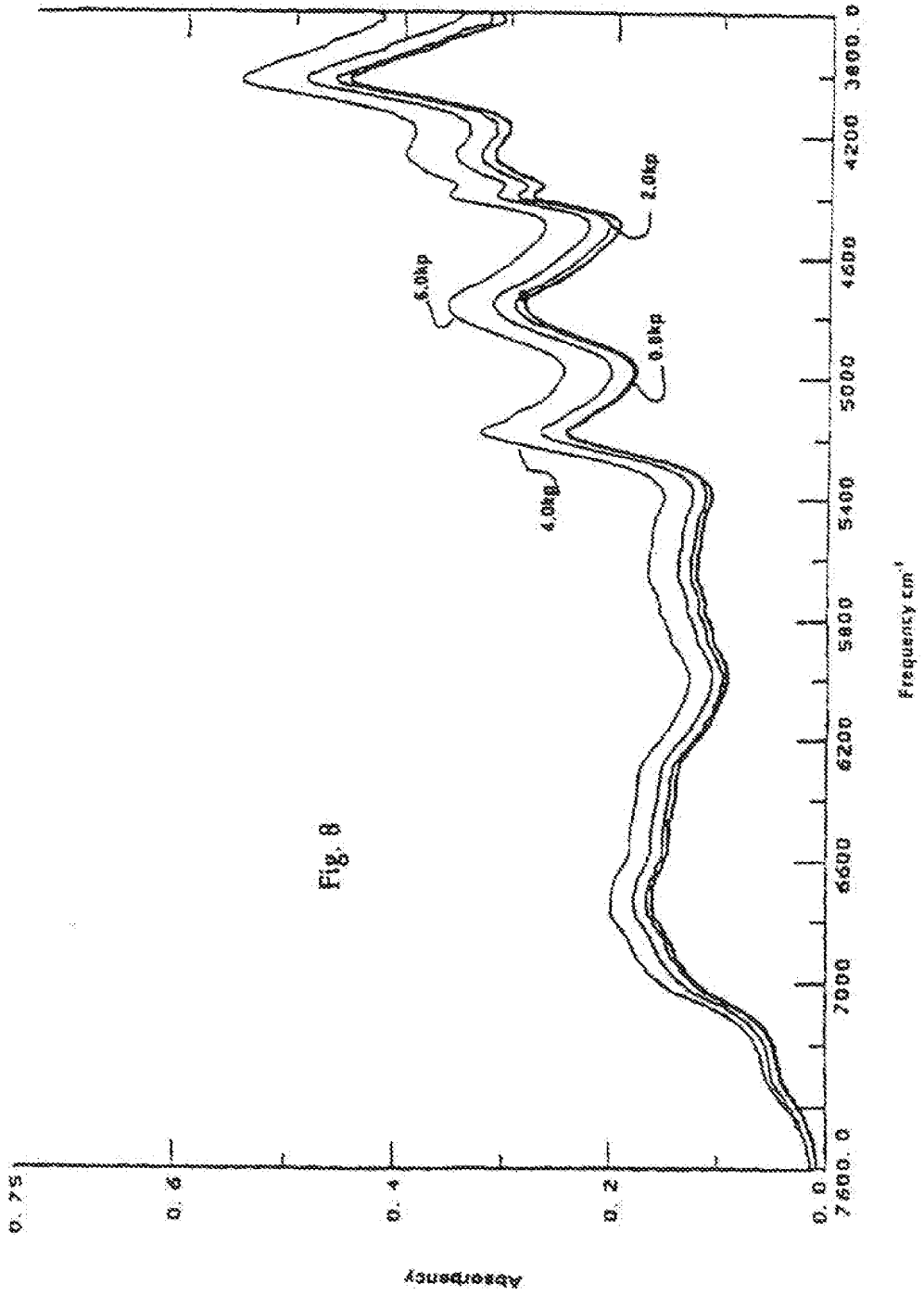
7000
6600
6200
5800
5400
5000
4600
4200
3800.0
Frequency cm⁻¹
2.8kp
6.8kp
0.8kp

Fig. 7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0.6
0.4
0.2
0.0
7600.0
7000
6600
6200
5800
5400
5000
4600
4200
3800.0
Frequency cm⁻¹
2.0kp
6.0kp
8.8kp
4.0kp

Fig. 8

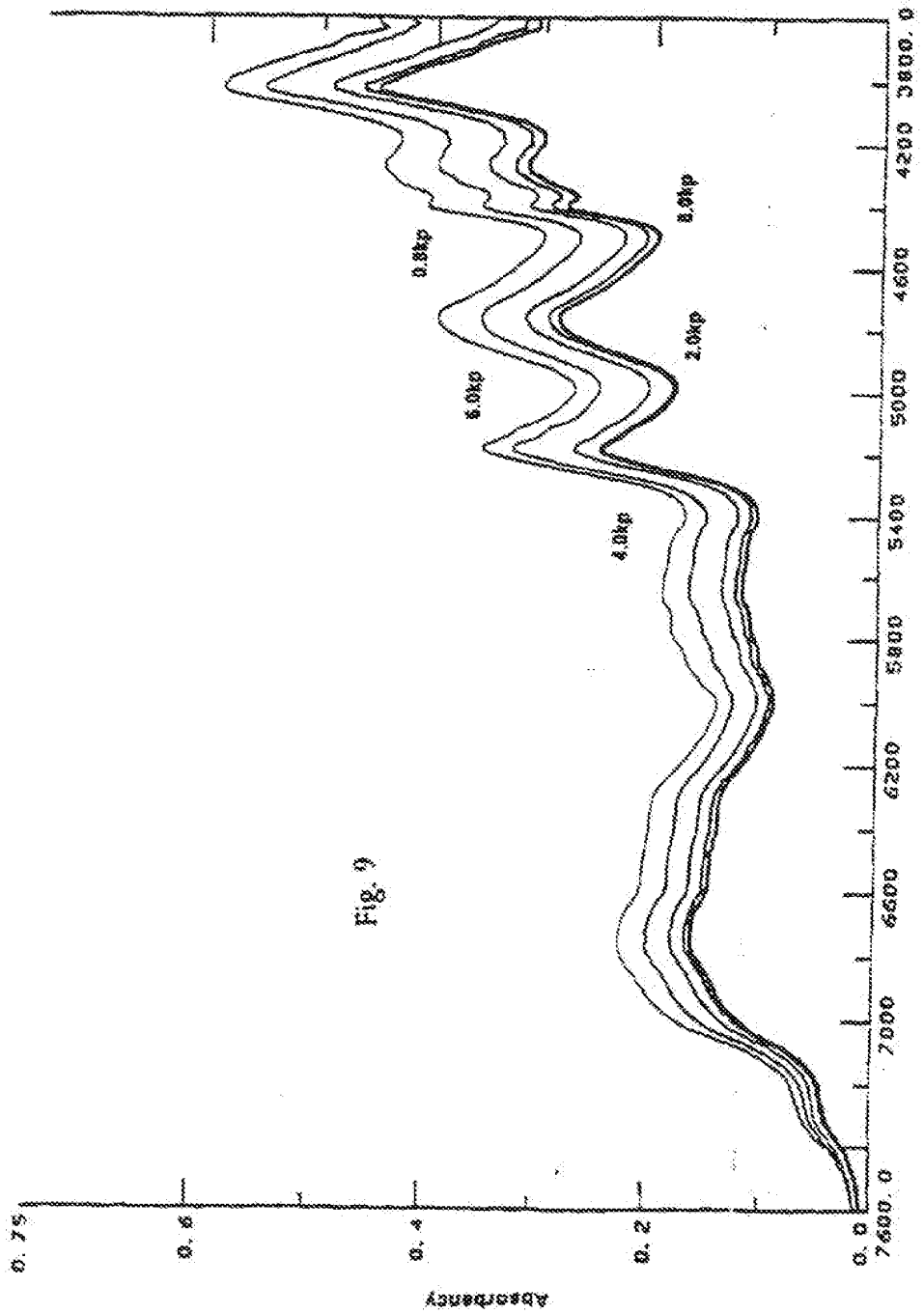

Fig. 9

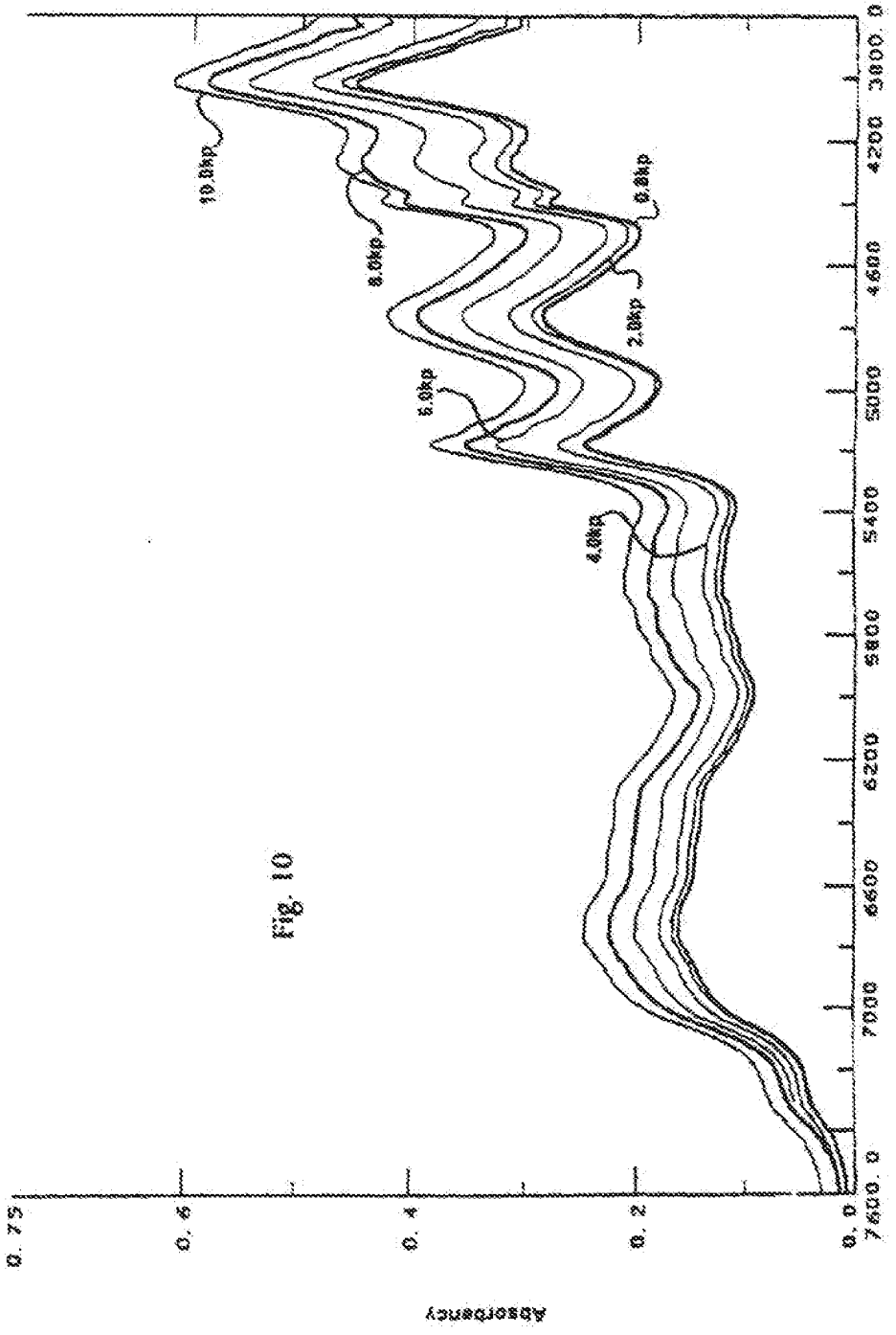

Fig. 10

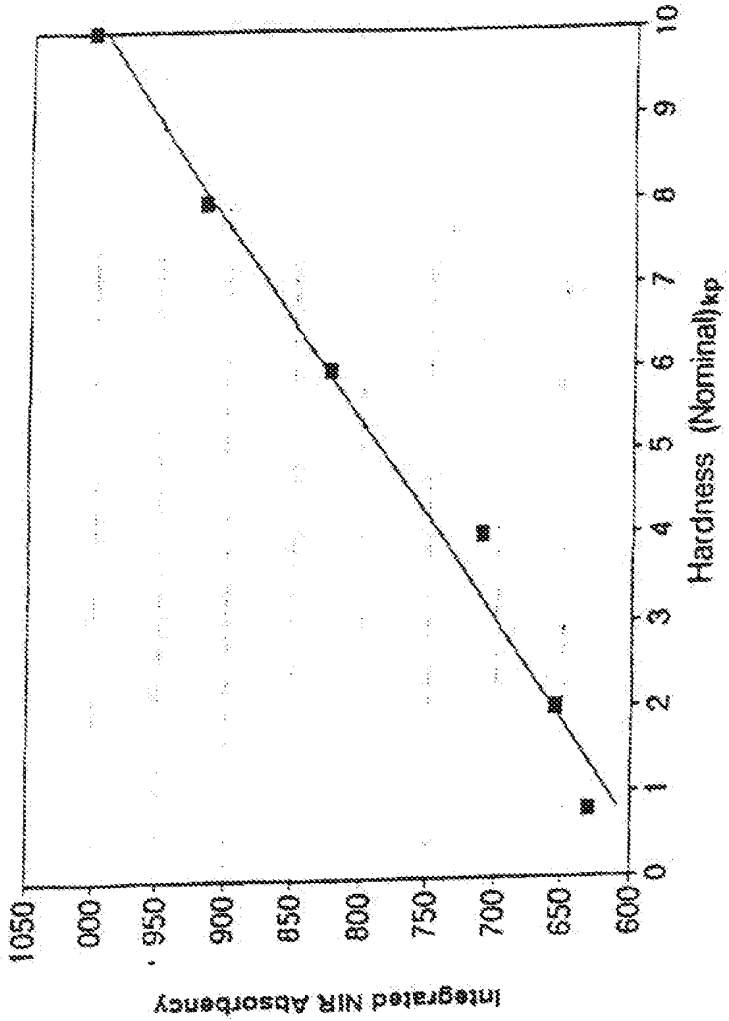
Integrated NIR Absorbency
1050
000
950
900
850
800
750
700
650
600
0
1
2
3
4
5
6
7
8
9
10
Hardness (Nominal)kp

Fig. 11

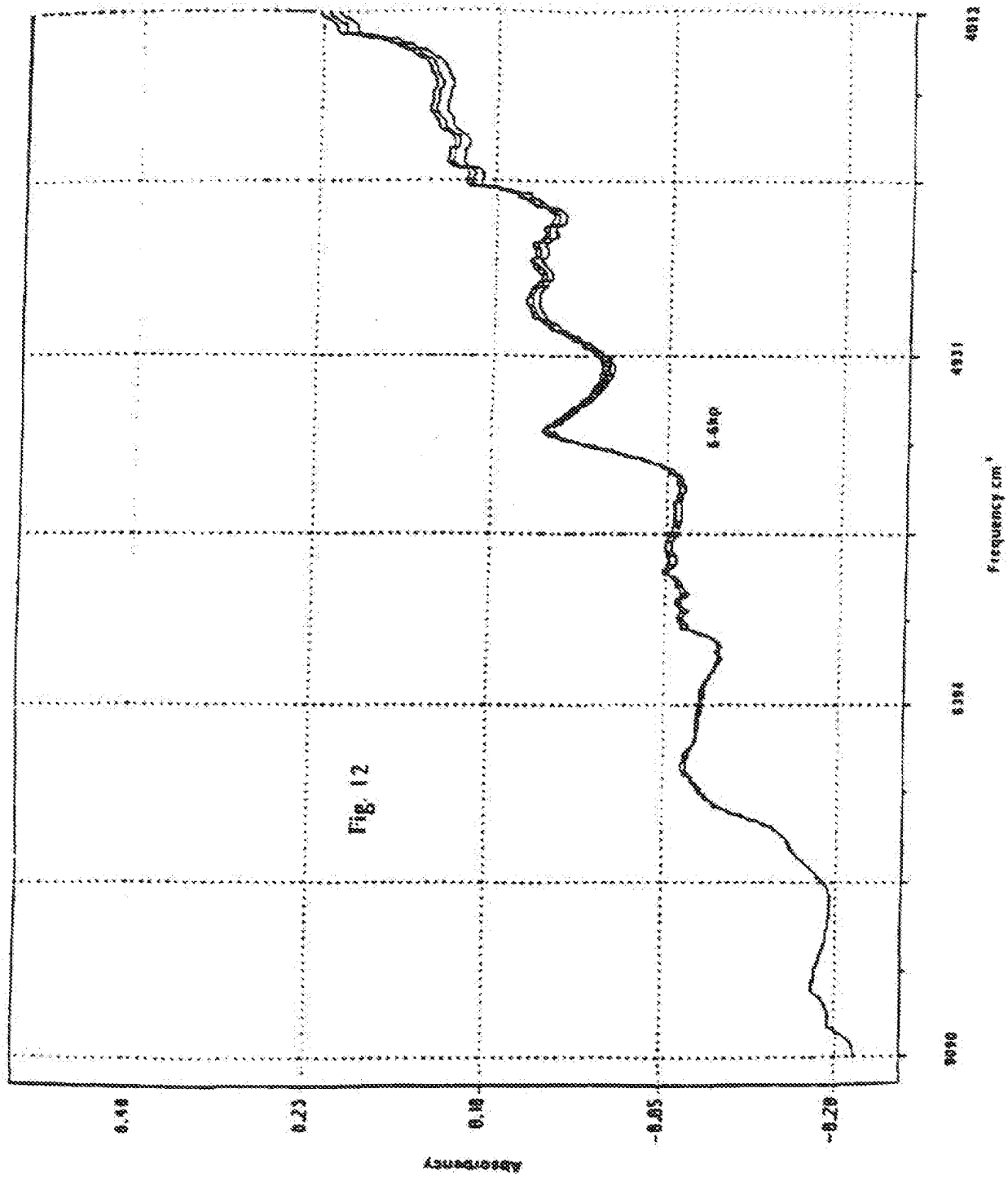

Fig. 12

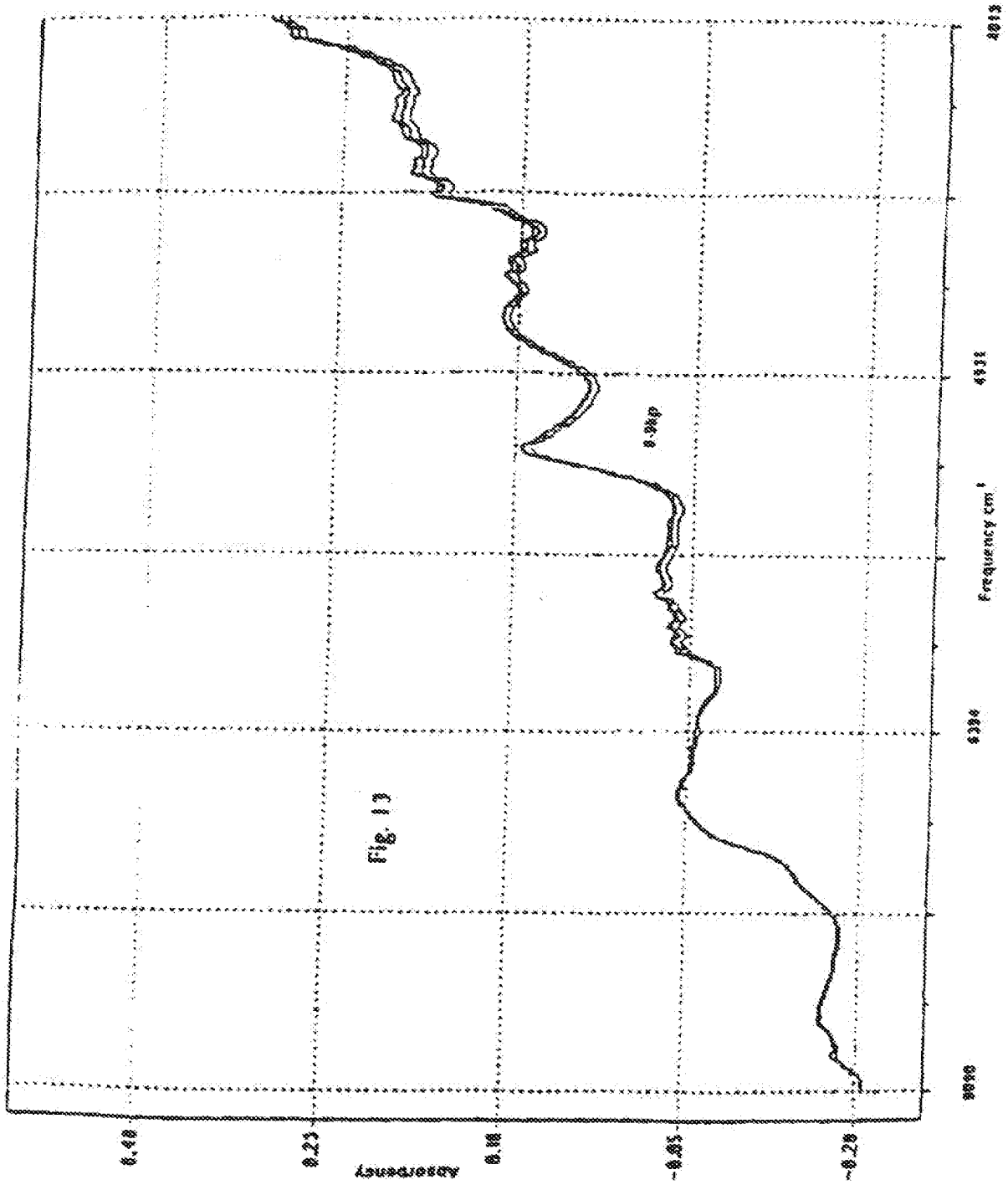

Fig. 13

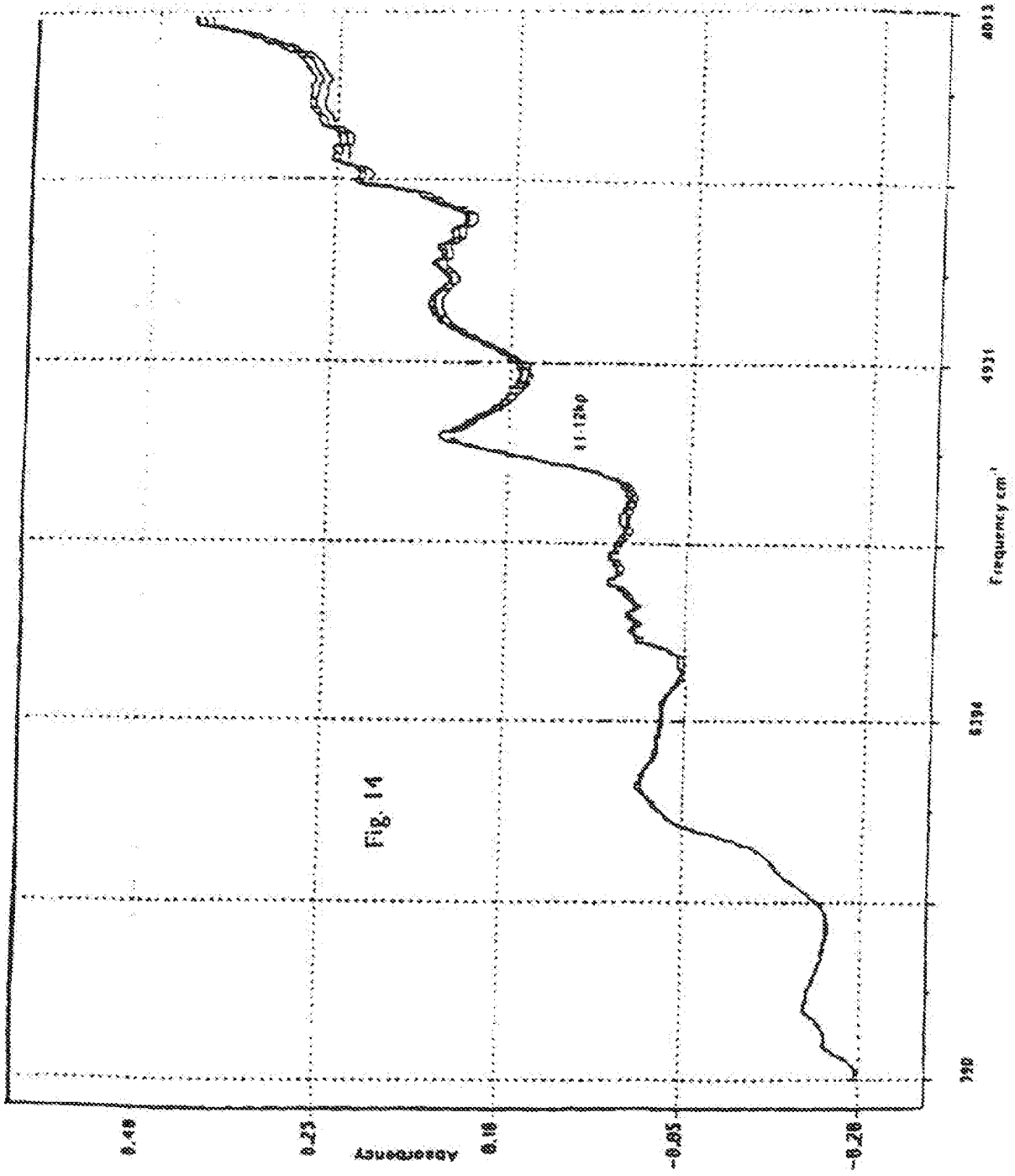

Fig. 14

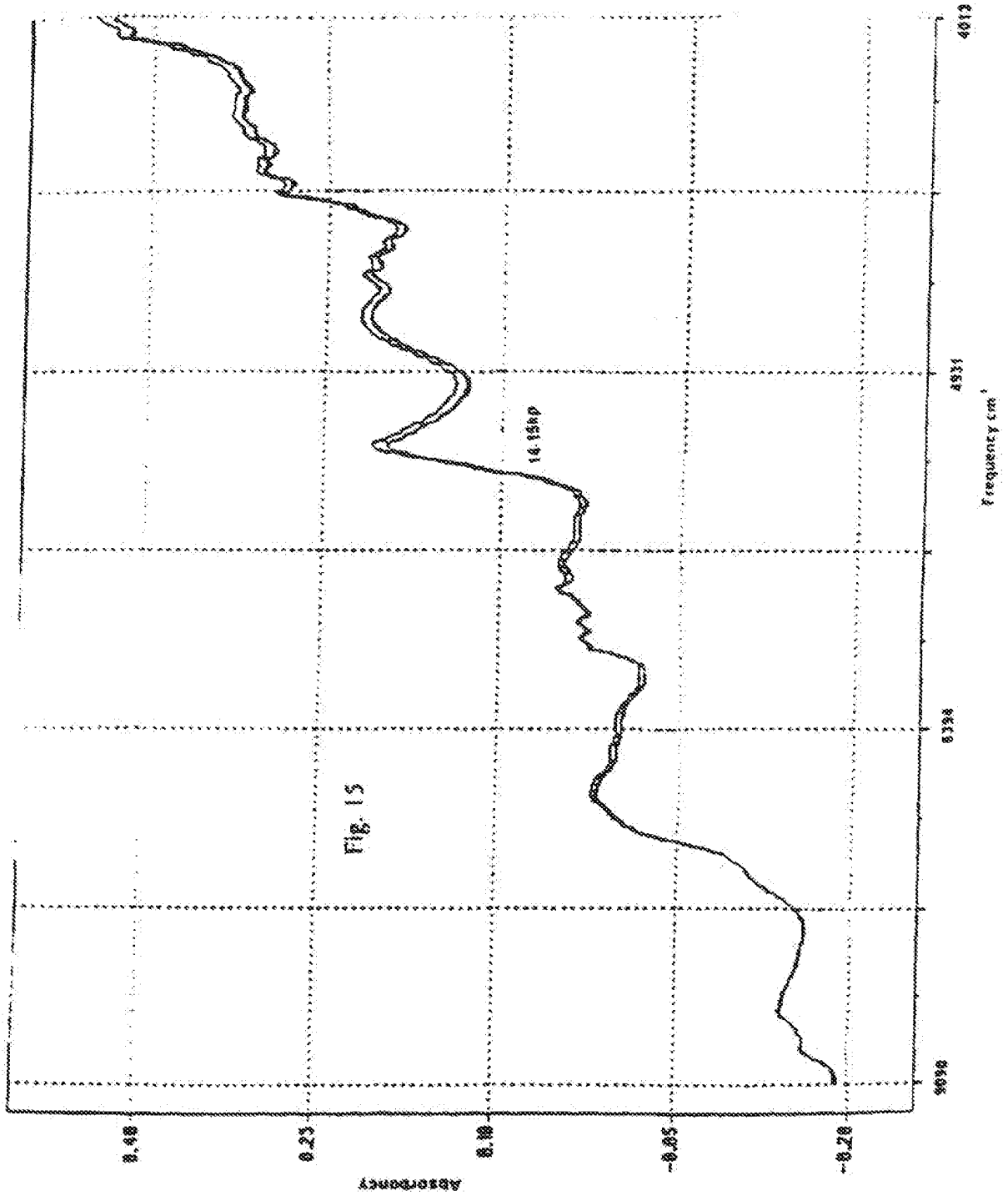

Fig. 15

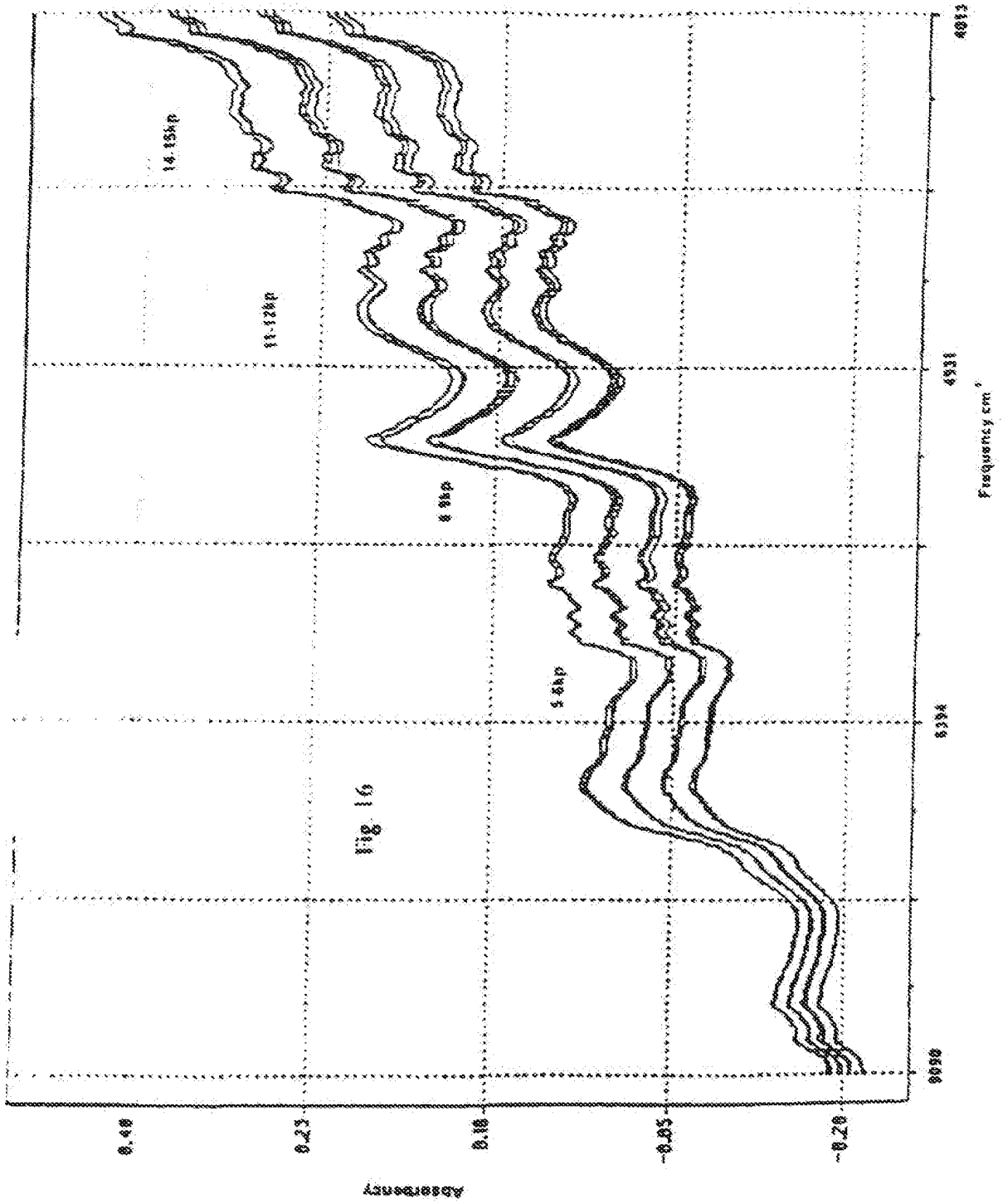

Fig. 16

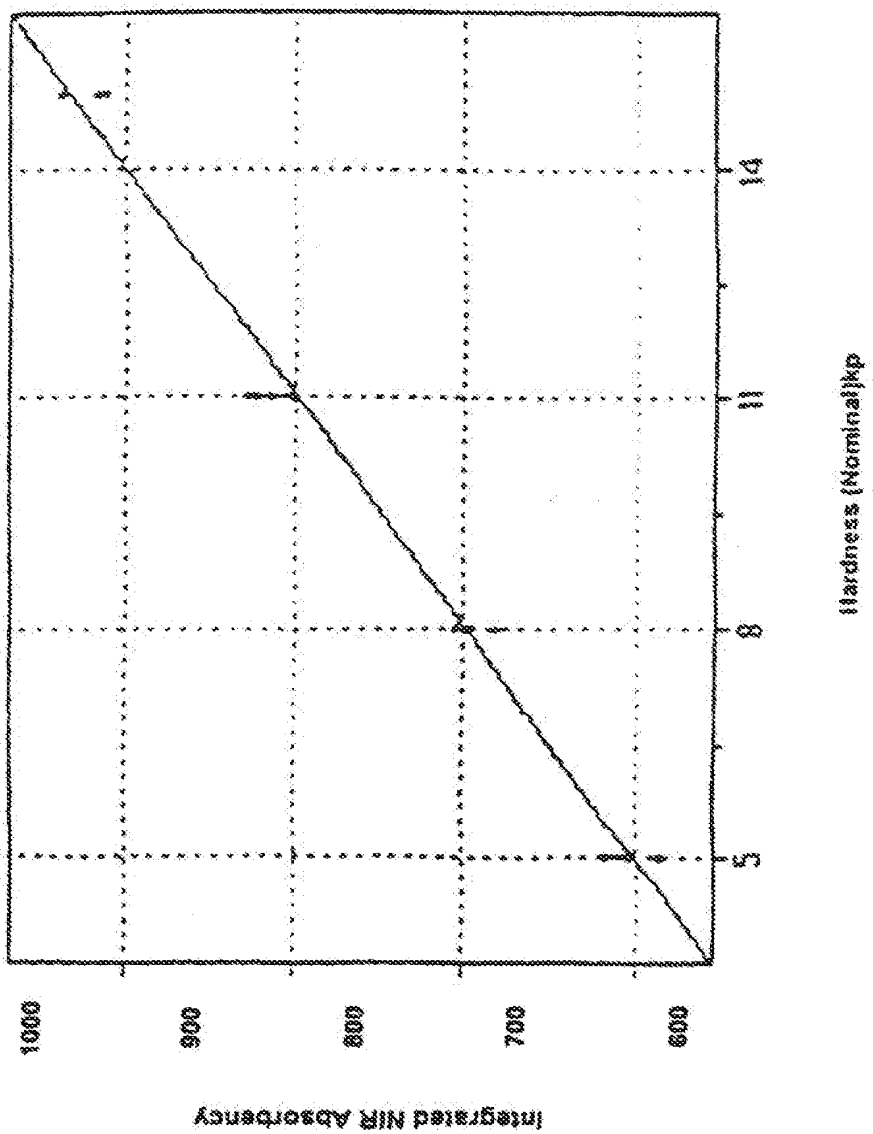

Fig. 17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14455

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :G01J 3/00, 5/08, 5/18
US CL. : 250/339.08, 339.11, 339.12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 250/339.08, 339.11, 339.12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS
search terms: infrared, spectrophotometer, conveyor,dissolution, probe, laser and optical switch

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,384,206 (BJARNO) 17 MAY 1983, ABSTRACT	1
A	US,A, 4,980,292 (ELBERT ET AL.) 25 DECEMBER 1990, ABSTRACT	1-5,9 AND 10
A	US, A, 5,089,701 (DULL ET AL.) 18 FEBRUARY 1992, ABSTRACT	1
A	US, A, 5,262,644 (MAGUIRE) 16 NOVEMBER 1993, ABSTRACT	1, 7, 11-15, 17 AND 20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 JANUARY 1996	16 JAN 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer VIRGIL O. TYLER Telephone No. (703) 305-7750

Form PCT/ISA/210 (second sheet)(July 1992)*

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(43) Date of A Publication 13.09.2000

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(22) Date of Filing 09.03.1999

(51) INT CL[7]
G01N 21/35

(52) UK CL (Edition R)
G1A AA4 AA6 ACDX AG13 AG17 AG6 AR6 AT20 AT3

(58) Documents Cited
GB 2326016 A GB 2292798 A US 5483223 A

(58) Field of Search
UK CL (Edition Q) G1A ACDL ACDX ADJS , G1B BCX
INT CL[6] G01N 21/31 21/33 21/35 21/39 33/15
ONLINE: WPI JAPIO EPODOC

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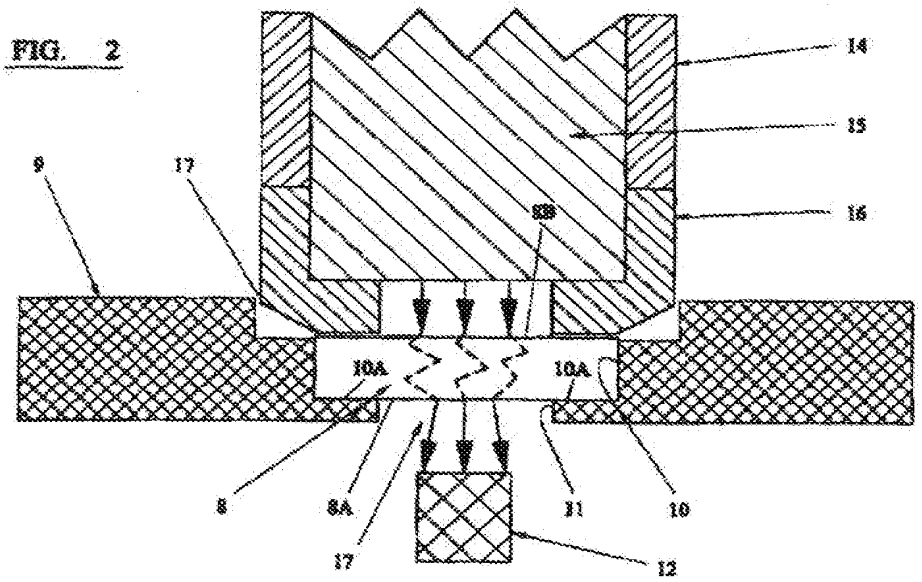
United Kingdom

(54) Abstract Title
Powder Analysis

(57) A method of analysing powder formed as a mixture of pharmaceutical ingredients and derived from a bulk preparation of powder by spectrophotometric analysis utilising transmission measurements. A sample powder is removed from the bulk mixture and pressed into a test wafer (8) and spectrophotometrically analysed to provide an assay test spectrum of actual absorption characteristics of ingredients in the material of the wafer (8). These characteristics of the assay test spectrum are compared with predetermined assay standard spectra determined from individual standard wafers of each relevant ingredient in the powder mixture by measuring absorption characteristics of the individual ingredients at known wavelengths of the beam to assess acceptability of the homogenity and distribution of the relevant ingredient in the powder of the sample. The wafer (8) is preferably pressed with flat and parallel opposed end faces through which the beam is directed.

FIG. 2



GB 2 347 739 A

At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

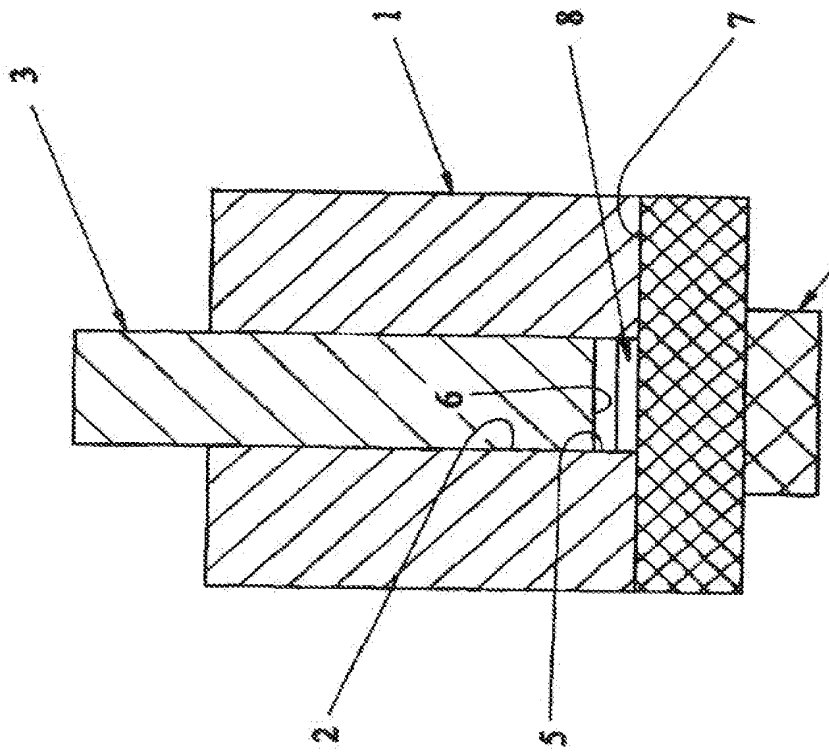


FIG. 1

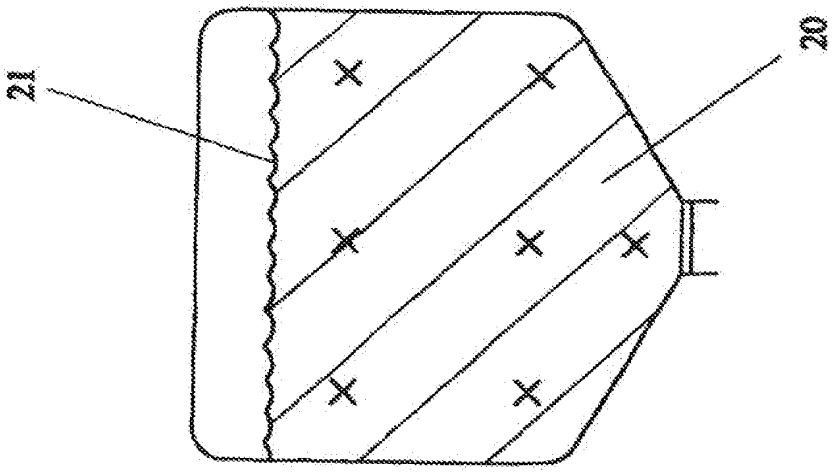


FIG. 4

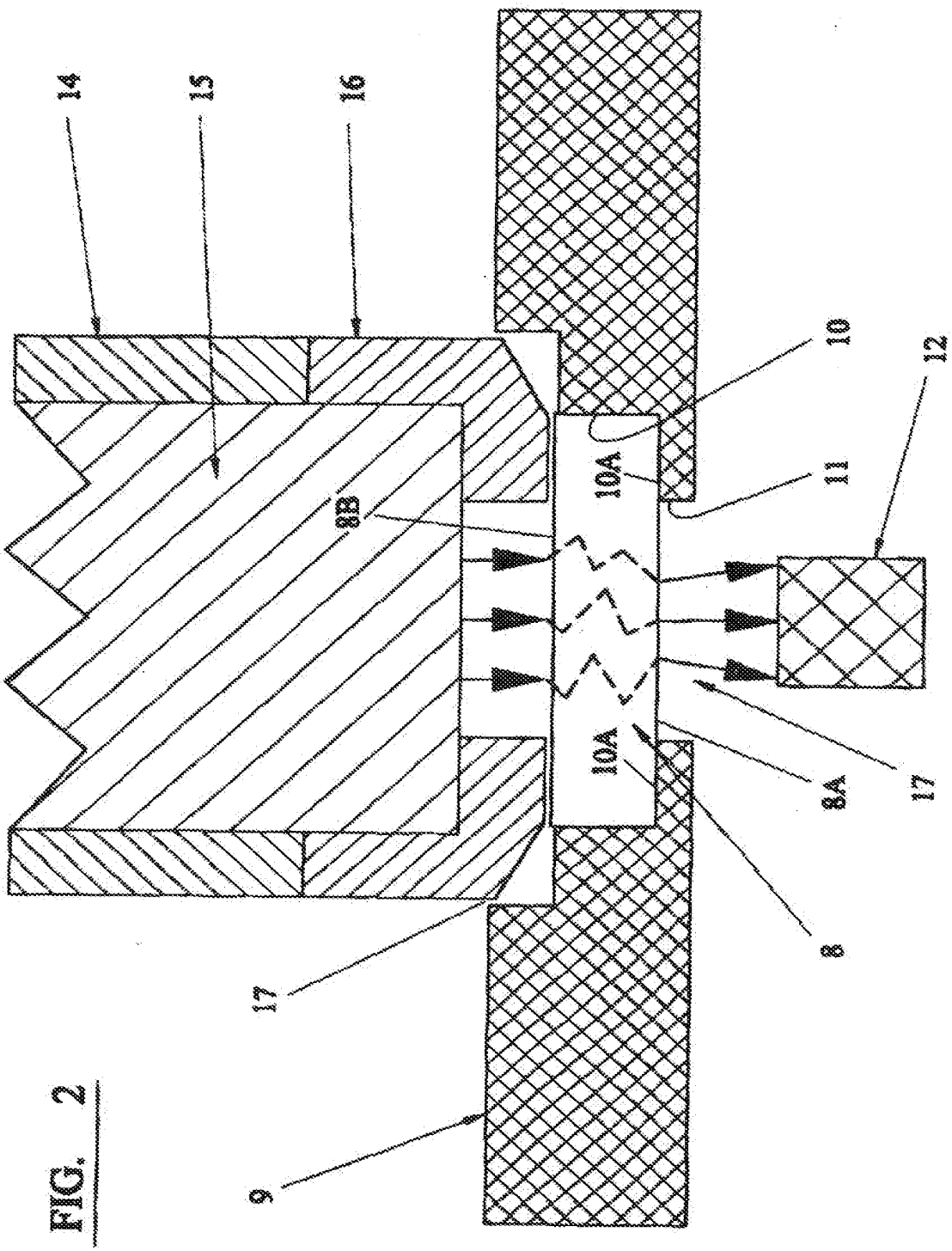


FIG. 2

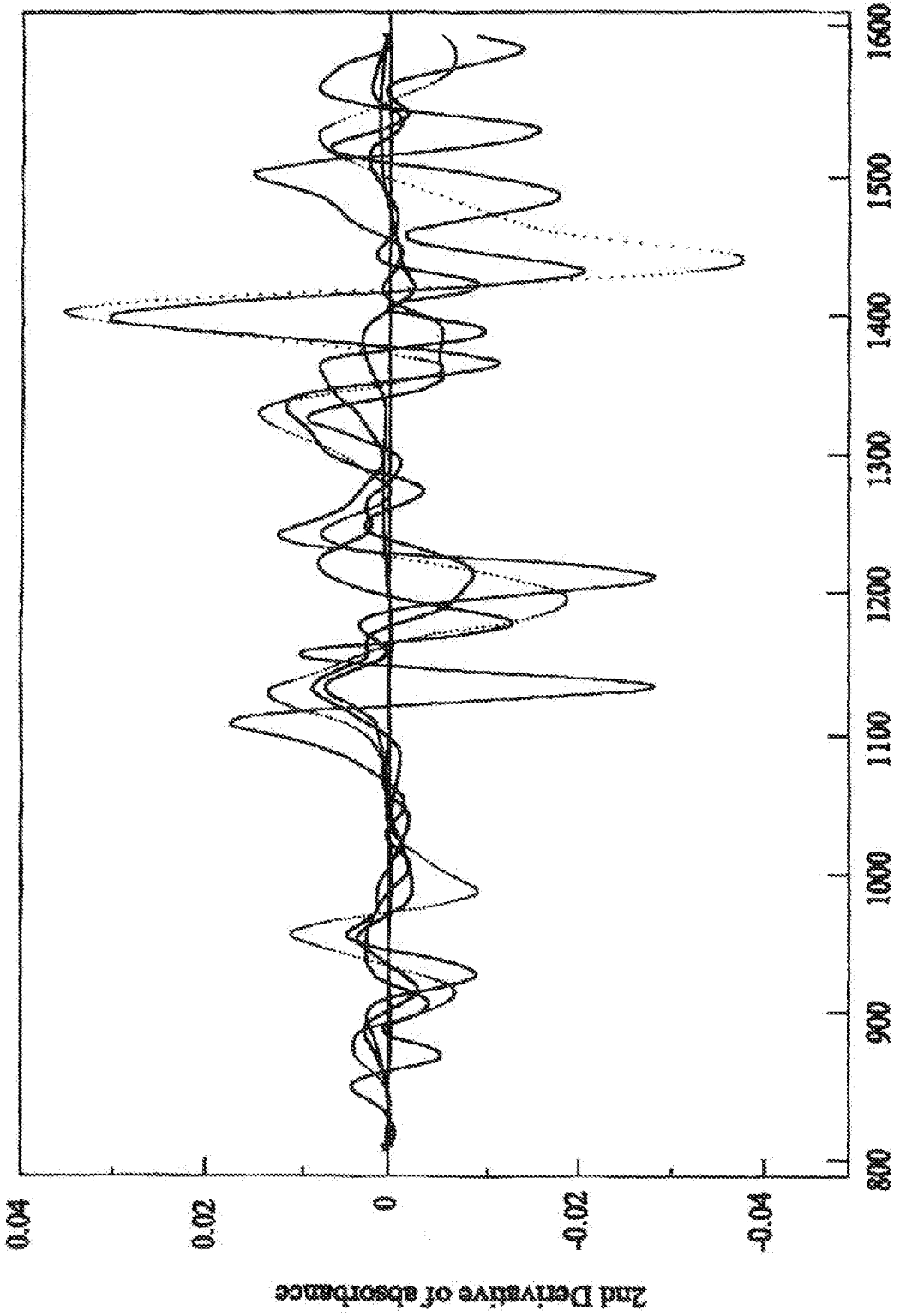


FIG. 3

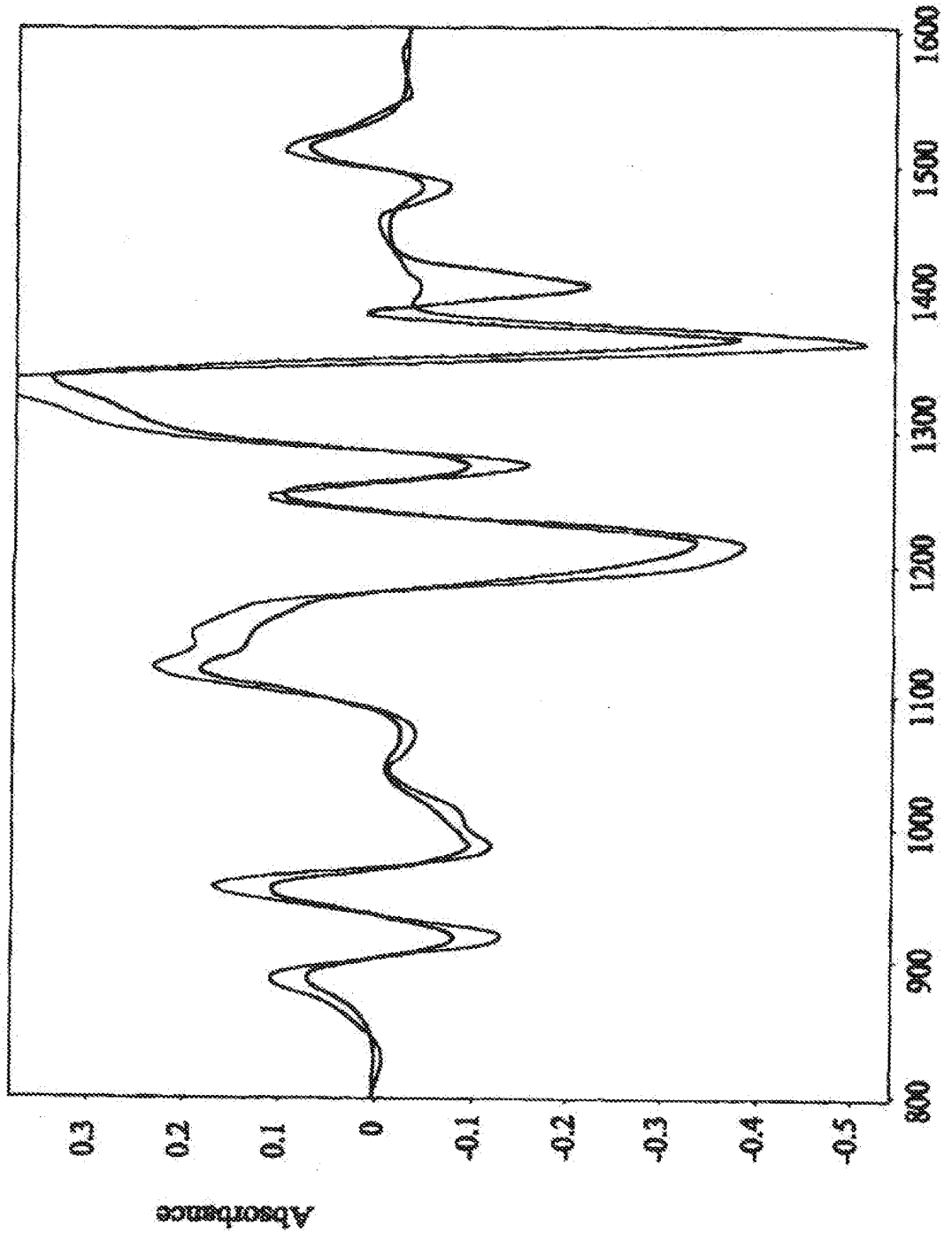


FIG. 3A

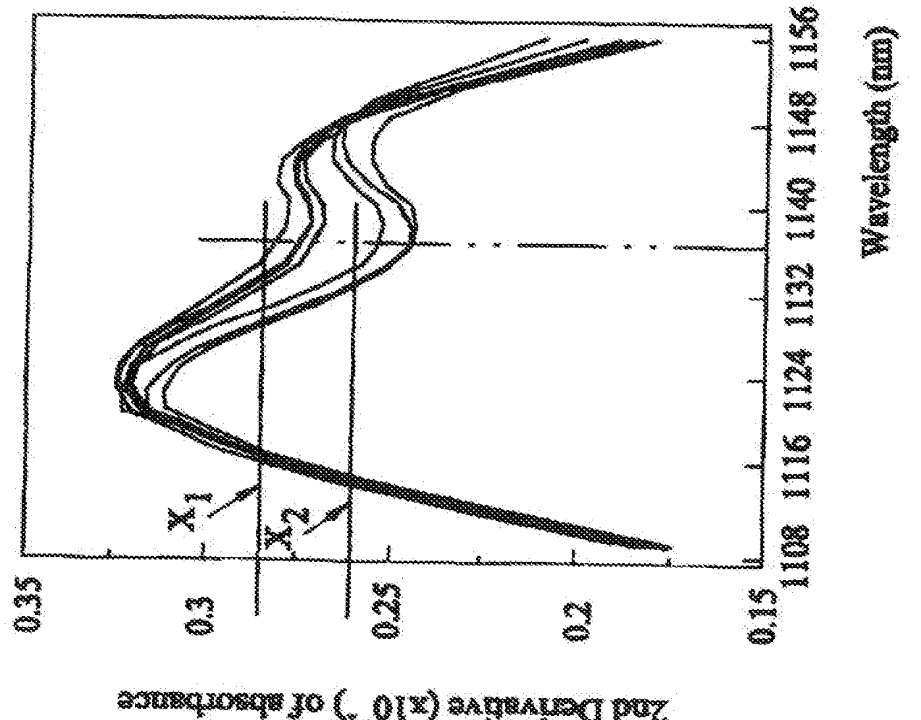


FIG. 5

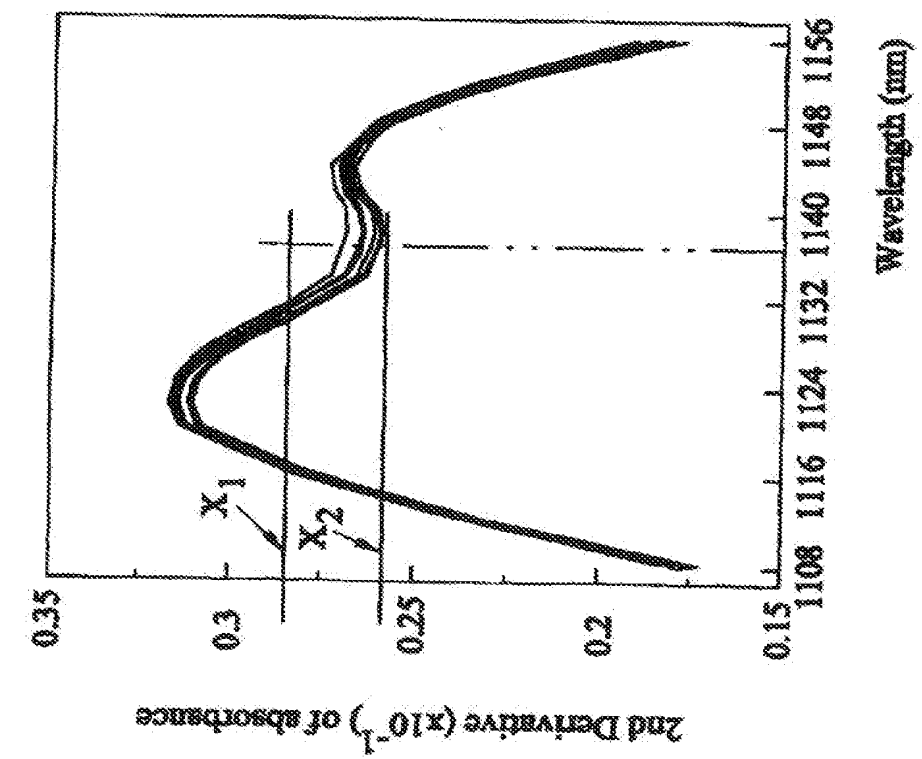


FIG. 6

POWDER ANALYSIS

Technical Field and Background Art

The present invention relates to powder analysis and is particularly concerned with a method of analysing powder formed as a mixture of ingredients and derived from a bulk preparation of such a powder.

The present invention was primarily, but not essentially, developed for use in the pharmaceutical industry where it is conventional practice in the commercial production of a product which is, or is to be derived from, a powder for the ingredients of that powder to be loaded into a mixing chamber where they are tumbled or otherwise agitated to ensure thorough mixing of the ingredients. For a pharmaceutical product, the powdered ingredients loaded into the chamber will be one or more active ingredients and one or more excipients. In a typical pharmaceutical facility, the bulk powder mixture will be in the order of 1000 kg and will be intended for sub-division, usually into small containers convenient for retail purposes, into capsules for individual doses of the powder or for processing into individual dose tablets.

Irrespective of the manner in which the bulk powder from the mixing chamber is subsequently processed to be presented for use or retail purposes, in the pharmaceutical industry there are statutory requirements that the ingredients in the form of the pharmaceutical or chemical constituents in end product (typically powder, capsules, or tablets as aforementioned) as presented for retail purposes or use are dispersed uniformly

throughout the material of the end product to ensure that dose formulations are identical within prescribed tolerances.

As a consequence, pharmaceutical products derived from powder are subjected to a qualitative and quantitative control analysis, principally to ensure that the end product has required chemical constituents, that the proportions of the required chemical constituents are correct and that the chemical constituents are dispersed uniformly throughout the end product. Where the bulk powder is processed into individual dose tablets, a conventional form of quality control is to subject tablets randomly selected from a production batch to spectrophotometric analysis where a beam of electromagnetic radiation (usually near infrared - NIR) is directed to and transmitted through the selected sample tablet for the transmitted beam to be detected and analysed. From variations in the absorption characteristics exhibited by the ingredients (chemical/pharmaceutical constituents) of the tablet to the applied radiation beam as measured by the detector, it is possible in known manner to effect the required qualitative and quantitative analysis.

Techniques for analysing tablets by NIR spectrophotometric transmission measurements are disclosed in our patent specification EP-A-0,896,215 and in EP-A-0767369.

Once production has started to sub-divide a bulk powder mixture into discrete weights or doses and to package those doses typically into capsules or to press them into tablets, production rates are so fast that if analysis of the final product indicates that the ingredients, particularly active

ingredients, are not uniformly dispersed throughout the bulk powder mixture, there is likely to be considerable wastage and expense (both in materials and in production), in the products which were made prior to a decision to stop production.

As a consequence (and in some countries it is a statutory requirement in the production of pharmaceutical products from powder mixtures), it is conventional practice to analyse samples of powder derived from the bulk mixture in the mixing chamber to ensure appropriate homogenity and concentration of the active and excipient ingredients within the bulk mixture before its sub-division commences. For this analysis several powder samples are taken from the bulk mixture at locations spaced from each other and at various depths in the mixture to give an overall picture of how well the ingredients are homogenised throughout the blend or mix.

Each powder sample that is removed from the bulk powder mixture is assessed for homogenity of its ingredients and conventionally this is achieved by either of two well-known techniques. The longest standing and probably most utilised technique is that of high performance liquid chromatography (HPLC) which is well-known in the art and as such need not be discussed in detail. However despite its popularity, it is recognised that HPLC has distinct disadvantages notably a) it utilises toxic solvents and therefore it has to be used in a facility remote from the chemical/pharmaceutical manufacturing facility for good manufacturing practice, b) the analysis can take many hours or days by experienced personnel with consequent expense and delays in production time, and c) it is suitable only for determining concentration throughout the

mixture of the or a particular active ingredient in the mixture.

The second technique is spectrophotometric analysis of the powder sample by reflectance measurements of a near infrared (NIR) beam. For each sample, a tablet dose weight is weighed into a glass vial or other container and the sample is then scanned. The sample is then mixed and scanned again - this procedure is repeated five times and the resultant spectra are then averaged. Spectrophotometric analysis of powder by reflectance measurements is discussed in connection with our patent publication WO 95/00831. The tablet dose weight is used for the analysis (although up to three times such a dose weight is permitted for the analysis) in accordance with regulations laid down by recognised pharmaceutical bodies on the basis that if a much larger weight from the sample is used, it could suggest that a mixture is properly homogenised when in fact it is not. The sample is scanned five times due the nature of the depth of penetration of the NIR light beam. Tests have shown that using standard NIR reflectance optics, the NIR beam will only pass into a fine white powder up to a depth of 0.5 mm. As a consequence, to get a representative view and useable cross section of the whole sample, the powder has to be mixed and scanned five times and the resultant spectra averaged. Homogenity of the mixture is then usually determined by calculating the standard deviation of the samples at absorption characteristics which are unique to the active ingredient or ingredients. The numerous scanning and re-mixing of powder from each sample is a lengthy procedure which causes consequential delays in production and is preferably carried out by experienced laboratory personnel. Overall therefore

this second technique of analysis is generally regarded as expensive and of suspect accuracy due to the inability of the NIR beam to scan efficiently a relatively thick surface layer of powder.

From the foregoing, it will be realised that there is a need to provide a method of analysing powder formed from a mixture of ingredients and prepared in bulk (particularly but not essentially for pharmaceutical and/or chemical products) and which method alleviates the disadvantages of the above described prior proposals. It is an object of the present invention to satisfy this need. More particularly, the present invention has as its aims to provide a method of analysing powder formed as a mixture of ingredients and derived from a bulk preparation which permits a fast analysis that may be used efficiently by inexperienced personnel to alleviate personnel error and delays in production and to provide an accurate analysis on the basis of which an assessment can be made on the acceptability or otherwise of the homogenity and concentration of either or both active ingredients and excipients in the bulk powder mixture or blend.

Statement of Invention

According to the present invention, there is provided a method of analysing powder formed as a mixture of ingredients and derived from a bulk preparation thereof which comprises predetermining an assay standard spectrum for a relevant ingredient of the bulk powder mixture by spectrophotometrically analysing characteristics of that relevant ingredient from transmission measurements of a beam of electromagnetic radiation applied to and passing through the relevant

ingredient to provide a spectrum of absorption characteristics at known wavelengths of the beam; removing a sample of powder from the bulk mixture and pressing powder of the sample into a self-supporting test wafer; spectrophotometrically analysing characteristics of the material of the test wafer from transmission measurements of the beam of electromagnetic radiation applied to and passing through the wafer to provide an assay test spectrum of actual absorption characteristics of ingredients in the material of the test wafer for known wavelengths of the beam, and comparing absorption characteristics from said assay standard spectrum with said assay test spectrum at predetermined wavelengths of the beam to assess acceptability of the relevant ingredient in the powder of the sample.

By the present invention, sample powder removed from the bulk mixture of powder ingredients as prepared for subsequent processing is subjected to spectrophotometric analysis by a beam of electromagnetic radiation (usually and hereinafter referred to as near infrared - NIR) that is transmitted through the material of the powder sample following that material being compressed into a self-supporting wafer.

The self-supporting characteristics of the wafer are intended so that the wafer may be handled relatively freely for fitting into the spectrometer without disintegrating. Typically the wafer will be formed with powder from an extracted sample amounting to approximately 0.5 to 1.5 (preferably 1.0) dose weight of tablets or capsules which may be intended to be produced from the bulk powder material. This powder dose weight may quickly and easily be compressed into a wafer

utilising a simple barrel and cylinder moulding press so that the wafer may be formed by unskilled operatives. Similarly such an unskilled operative may locate the wafer in a wafer holder of a spectrometer and actuate the spectrophotometric system to provide the required assay test spectra.

Relevant ingredients, be they either active or excipient, in the bulk powder mixture will be known and each relevant ingredient is subjected to spectrophotometric analysis to provide an assay standard spectrum. This assay standard spectrum is preferably achieved by use of a self-supporting standard wafer of the respective relevant ingredient similarly sized to the test wafer formed from the bulk powder sample. By comparing the assay test spectrum of the actual absorption characteristics of ingredients in the material of the test wafer formed from the sample of the bulk powder material with the assay standard spectra of the relevant ingredients it is possible to assess the quantitative presence of the relevant ingredients in the powder sample. This latter assessment may also be made by unskilled personnel quickly and efficiently.

It is also possible to provide the required assay standard spectrum from a sample of powder which includes the relevant ingredient and which sample has already been determined as being accurate in the quantity and distribution of the relevant ingredient, for example, by HPLC. This validation of the accuracy of the spectroscopy by comparison with chromotographical testing is likely to require skilled personnel, but having once determined the assay standard spectrum that data is available for use by unskilled personnel in carrying out the method of the present invention.

In practice, it will be usual for an operative to remove two or more samples of powder from spaced locations (both horizontally and vertically) in the bulk mixture and to press similar self-supporting wafers from the samples and to provide assay test spectra for the respective wafers. Absorption characteristics from the assay standards are then compared with the respective assay test spectra at appropriate wavelengths of the beam to assess acceptability of the distribution and the concentration of the relevant ingredients throughout the bulk mixture. It will be appropriate for experienced or skilled personnel to determine permissible tolerances in the distribution of the relevant ingredients but once these have been set, it is possible for an unskilled operator to quickly determine whether the homogenity of the distribution of respective ingredients throughout the bulk powder mixture is acceptable for that mixture to proceed to further processing such as tableting or encapsulation of individual dose weights.

The method of the present invention will permit analysis of the bulk powder mixture to be effected by unskilled personnel quickly and efficiently in the vicinity of a production facility for good manufacturing practice thereby alleviating considerable expense which may otherwise be incurred from lengthy delays in production frequently caused by use of conventional analysis techniques.

A preferred feature of the present invention is that the powder of the sample is pressed into a wafer having flat, parallel and opposed end faces and that the NIR beam is directed perpendicularly through those flat end faces. Such a flat faced wafer is advantageous in that it provides efficient

transmission characteristics for the NIR beam to be effective over a wide band wavelength in the spectrum of the transmitted beam. In comparison, conventional tablets tend to have convexly curved opposed end faces on which may be embossed or engraved trade marks or other indicia and when such tablets are subjected to spectrophotometric analysis by transmission it is found that the resultant spectrum from the transmitted beam is useable over a relatively narrow wavelength band due to light scatter and stray light resulting from the convex and possibly undulating profile presented by the opposed end faces of the tablet.

Furthermore, by use of a flat faced wafer, it is convenient and efficient to mount the wafer in a holder of the spectrometer with flat faces in face to face contact to alleviate stray light from the applied or incident NIR beam from being directed into the detector between the wafer and the wafer holder (rather than by passing through the material of the wafer).

A further advantage of the present invention is that in a production facility where the bulk powder mixture is to be processed into tablets, the spectrometer and detector as used for the analysis of the material in the wafer derived from the powder sample can also be used for spectrophotometric analysis of tablets produced from the powder mixture in accordance with the disclosure in our patent specification EP-A-0,896,215.

Drawings

An embodiment of the method of analysing powder in accordance with the present invention will now be described by way of

example only, with reference to the accompanying illustrative drawings in which:

- Figure 1 diagrammatically shows part of a moulding tool for forming a wafer to which the method of the invention is to be applied;
- Figure 2 diagrammatically shows a side elevation, in part-section, of a spectrophotometer for use in analysing characteristics of a wafer derived from the mould of Figure 1;
- Figure 3 shows absorption spectra for individual relevant ingredients in a bulk powder mixture which is to be analysed in accordance with the method of the invention;
- Figure 3A compares absorption spectra derived from a wafer and from a tablet pressed from the same sample powder;
- Figure 4 diagrammatically illustrates powder in a bulk mixing chamber and indicates typical locations at which seven samples of the powder are taken for analysis;
- Figure 5 shows absorption spectra which may be derived from seven wafers formed from the powder samples taken from the mixing chamber of Figure 4 and which samples are considered to be unacceptable for ingredient distribution; and
- Figure 6 shows absorption spectra similar to that of Figure 5 and which permits a conclusion that ingredient distribution throughout the powder mixture is acceptable.

Detailed Description of the Drawings

The present invention utilises spectrophotometric analysis by transmission of ingredients in a wafer 8. The wafer is formed by compression of sample powder derived from a bulk powder

mixture and for the purpose of forming the wafer 8 from powder by a non-skilled operative, a simple moulding tool is provided and shown in Figure 1. The mould has a barrel 1 within a through cylinder 2 of which is slidably located a complementary cylindrical plunger 3. The plunger 3 projects from one end of the cylinder 2 and the opposite end of the cylinder is closed by a removable base 4. A cylindrical moulding chamber 5 is thus defined within the cylinder 2 between a flat radially extending end face 6 of the plunger 3 and an opposing flat parallel face 7 of the base 4.

The wafer 8 is formed by removing the plunger 3 from its cylinder 2 and loading into the cylinder 2 a predetermined weight of powder from which the wafer 8 is to be formed. The powder is distributed uniformly over the face 7 within the cylinder 2 and the plunger 3 inserted into the cylinder for its flat end face 6 to lie on the powder.

The assembly as shown in Figure 1 is now fitted within the jaws of a press or torque wrench (not shown) by which the plunger 3 is driven along its cylinder towards the base 4 to compress the powder into the wafer 8. It is intended that the wafer 8 when removed from the moulding chamber 5 (simply by opening that chamber on removing the base 4 from the barrel 1) should be self-supporting so that if it can be handled reasonably freely for mounting in a spectrometer. To provide self-supporting wafers from typical pharmaceutical powders, it is preferred that the powder is subjected to a compressive force of at least 175 kg per square centimetre, more preferably 211 kg per square centimetre.

The wafer when removed from the press will have a cylindrical profile with parallel and opposed flat end faces which extend perpendicularly from the axis of the cylinder. The cylinder 2 will usually have a diameter in the range of 0.8 to 2.5 cm as considered appropriate for the amount of sample powder which is to be loaded into the moulding chamber 5 so that the wafer will be of adequate thickness to be self-supporting.

Figure 2 diagrammatically shows part of a spectrophotometer for analysing characteristics of the material of the wafer 8 by measurements from a beam of near infrared radiation (NIR) transmitted through the wafer. Conveniently, the spectrophotometer will be considered as that sold under the trade mark INTACT™ of Foss Electric. The spectrophotometer has a wafer holder 9 with a cylindrical recess 10 which is complementary to the cylindrical form of the wafer 8 and which recess 10 is co-axial with a circular aperture 11 in the wafer holder. Sited below the aperture 11 is a detector 12 from which spectra measurement signals are derived in known manner. The cylindrical recess 10 is concentric with a cylindrical probe 14 housing a fibre-optic bundle 15 through which the NIR beam is to be directed from its source. The probe 14 is longitudinally displaceable in the direction of its axis for its tip 16 to be received as a close sliding fit in a cylindrical recess 17 in the wafer holder which recess 17 is concentric with and extends from the recess 10. A wafer 8 which is to be subjected to analysis is located in the complementary recess 10 with one of its flat end faces 8a in face to face abutment with a flat annular bottom face 10a presented in the bottom of the recess 10.

For an analysis measurement, the probe tip 16 is moved into face to face abutment with the second flat face 8b of the wafer 8 following which a beam 17 of NIR radiation is directed from the probe tip to be transmitted through the wafer by way of its flat end faces 8a and 8b to be applied to the detector 12 and provide measurements from which absorption spectra of the wafer material are derived.

From Figure 2, it will be seen that the complementary seating of the wafer 8 in its cylindrical recess and in face to face abutment with the annular bottom face 10a alleviates stray light from passing between the wafer and its holder to the detector 12. The face to face abutment between the probe tip 16 and the wafer 8 also alleviates stray light passing through the wafer to the detector. Whilst the force of abutment between the probe tip and wafer may be light, it should be ensured that the self-supporting characteristics of the wafer are adequate for the wafer to withstand the abutment without material disintegration. This abutment will also urge the wafer into abutment with the face 10a of the wafer holder.

The method of the present invention was developed primarily for analysing pharmaceutical powder to determine whether or not active ingredients and possibly excipients in the powder are distributed uniformly/homogeneously throughout the bulk of the powder. This is achieved by reference to absorption spectra derived from the transmission of the NIR beam 17 through wafers 8 formed from samples of the bulk powder mixture per se and by reference to similar absorption spectra from assay standard wafers each of which is for a relevant ingredient of the bulk powder mixture. In the present example, it may be assumed that

the bulk powder mixture has five relevant ingredients comprising one active and four excipients such as a sugar, a phosphate, a glycolate and a sterate. Five wafers 8 are produced one for each of these five relevant ingredients.

Usually the assay standard wafers as aforementioned will be formed from a weight of the relevant ingredient approximating to the dose weight of tablets or capsules into which the bulk powder mixture is to be processed. Each of the assay standard wafers 8 of the relevant ingredients is then subjected to analysis by the spectrophotometer shown in Figure 2 to provide a spectrum showing variations in absorption by the relevant ingredient of the NIR beam for different wavelengths. These absorption characteristics are mathematically treated in known and conventional manner to provide a second derivative which can be plotted against wavelength.

Figure 3 shows five graphs, one for each of the wafers of the five relevant ingredients in the bulk powder mixture under consideration to provide an assay standard spectra. It will be seen from Figure 3 that the useful assay standard spectra extends over a broad band of wavelength (800 to 1600 nm) in the NIR beam and this is believed to be attributable, to a substantial extent, by use of flat parallel faces of the wafer through which the beam is transmitted to the detector so that this transmission may be achieved efficiently (particularly in the absence of stray or spurious light).

The provision of such a usefully wide or broad band spectrum as shown in Figure 3 has the advantage that a wide range of wavelengths can be studied for absorption characteristics of

active or excipient ingredients in the test wafer under consideration. It will be noted from Figure 3 that different ingredients may peak predominately over other ingredients in a second derivative of their absorbance at different wavelengths so that these distinctive peaks can be utilised to provide readily discernable points in the assay standard spectra against which assay test spectra derived from samples of the bulk powder material may be compared.

Advantages of using flat faced wafers 8 as aforementioned will also be appreciated from Figure 3A which shows two graphs of absorbance against wavelength. Graph A (chain dotted line) is the spectrum derived by the transmission of the NIR beam through the flat faced wafer formed from a powder sample as previously described. Graph B (uniform line) is the spectrum derived by the transmission, in similar circumstances, of the NIR beam through a conventional shape of tablet pressed from the powder sample, the tablet being of a lozenge shape with opposed part convex faces having bevelled edges. The opposed faces of the tablet were embossed with a trade mark and dosage weight respectively. The tablet and wafer wave of substantially the same weight. It will be apparent that the deviation of absorbance for the wafer (Graph A) is less than that for the tablet (Graph B). This indicates that the absorption demonstrated by the tablet can be too strong to permit adequate light transmission for accurate measurement. For certain wavelengths, particularly larger IR wavelengths as shown by Graph B, it is unlikely that any light will be transmitted through the tablet - this is partly due to the non-flat profile which the faces of the tablet present to the NIR beam and the resultant scatter effect which the tablet shape

produces. In comparison, scatter is very much reduced for the flat faced wafer and it is possible to determine the thickness of the wafer to permit a wider range of wavelengths transmission (and therefrom provide a broader useful spectrum) in comparison with that provided by the tablet.

Figure 4 shows a mixing chamber 20 which is loaded with the previously mentioned five relevant ingredients/components in the proportions and weights as may be required for the pharmaceutical/chemical mixture, particularly for non-pharmaceutical applications where regulations may permit. The powders in the chamber 20 are thoroughly mixed by tumbling or otherwise to provide a bulk powder mixture in which it is necessary for the relevant ingredients to be dispersed uniformly and homogeneously throughout the mixture 21 prior to that mixture being further processed to provide single dose tablets or capsules. In a typical pharmaceutical production process, the powder mixture 21 may amount to 1000 kg.

For analysis purposes, several samples of powder 21 are now removed from the bulk mixture at various spaced locations throughout the breadth and depth of the bulk powder. Typically seven samples will be taken from the powder 21 at locations indicated by the small crosses in the mixing chamber 20 so that such samples should provide a fair representation of the manner in which the relevant ingredients are dispersed throughout the whole of the bulk mixture 21. Preferably, each of the samples corresponds approximately to the dose weight of the tablet or capsule which is intended to be formed from the bulk powder, typically 0.25 grams, although such samples are likely to be in the range of 0.22 to 1.0 grams. The powder of the seven

samples taken as aformentioned is formed into seven discrete test wafers 8 as previously described. Each test wafer from the sample is then subjected to spectrophotometric analysis in a similar manner to the analysis of the standard wafers for the individual relevant ingredients to provide assay test spectra of the absorption characteristics for various wavelengths in the NIR beam.

A particular advantage of analysing the material of the standard and test wafers spectrophotometrically by transmission of the NIR beam through the thickness of the wafer is that it provides accurate spectra which is indicative of the ingredients throughout the thickness of the wafer so that, in practice, it is only necessary to scan each wafer once in the spectrometer (as compared with the minimum of five scans required when analysing powder spectrophotometrically by reflectance techniques).

Figure 3 shows that the spectrum for one of the five ingredients has a prominent absorption peak for the beam wavelength 1136 nm and this peak is conveniently used as a reference for that particular ingredient in carrying out the analysis. From the assay test absorption spectra of actual absorption characteristics of the seven test wafers derived from the samples of bulk powder as shown in Figure 5 (which is conveniently over a narrow band wavelength which includes the 1136 nm relevant wavelength), it will be seen that at the 1136 nm wavelength, the lines of the spectra extend over the absorbant range 0.024 to 0.028. Although only six spectral lines are shown at the 1136 nm wavelength whilst seven spectral lines would be expected from the seven assay test wafers, it

will be appreciated that two of the spectral lines are substantially coincident with each other (as indicated by the presence of a relatively thick line).

For the particular ingredient whose absorbance characteristic peaks at the 1136 nm wavelength, it is determined, empirically or otherwise, that for such ingredient to be homogeneously and uniformly dispersed throughout the bulk powder mixture, it is necessary for its second derivative of absorbance (as shown by the spectra of Figure 5) to be within the tolerance range 0.026 to 0.028 (as indicated by the lines X1 and X2 in Figure 5). The spectra of Figure 5 clearly indicate that the spread of absorbance demonstrated by the ingredient relevant to the 1136 nm wavelength from the seven samples within the bulk powder mixture falls well outside of the acceptable tolerance range indicated by the lines X1 and X2 so that bulk powder mixture is unacceptable for further processing.

This conclusion may be determined quite readily and quickly by unskilled personnel instructed in the preparation of the test wafers, the loading of these into the spectrometer and the interpretation of spectra produced similar to that shown in Figure 5. The operative can then, if necessary, submit the bulk powder to further mixing and prepare a further set of assay test wafers to provide further assay test spectra until such spectra may be similar to that shown in Figure 6 where, at the 1136 nm wavelength, all of the spectral lines are within the absorbance tolerance range between the lines X1 and X2 indicating that, at least as far as the particular relevant ingredient as aforementioned is concerned, the homogenity and uniformity of the mixture is acceptable.

It will be appreciated that all five of the relevant ingredients from which the spectra of Figure 3 was produced will be assessed similarly from the seven test wafers to ensure that the homogenity and uniformity of all five relevant ingredients throughout the bulk powder mixture is acceptable.

As a consequence of the present invention, it is possible for unskilled personnel quickly, efficiently and economically to:

a) essentially identify that the correct product or ingredient is present in the bulk powder mixture by ensuring that the specific absorption characteristics (for example the peak at 1136 nm in Figure 3) for that product appear in the assay test spectrum;

b) show that the concentration of the relevant ingredient is as required from the intensity of the absorption indicated in the assay test spectrum for that ingredient (for example the intensity indicated by the aforementioned peak at 1136 nm); and

c) assess how well the relevant ingredient has been mixed (homogenity) throughout the bulk powder mixture from variations in the absorbance at predetermined wavelengths for identical wafers produced from several samples of powder taken throughout the bulk powder mixture (for example the seven samples assessed at the aforementioned peak of 1136 nm in Figures 5 and 6).

CLAIMS

1. A method of analysing powder formed as a mixture of ingredients and derived from a bulk preparation thereof which comprises predetermining an assay standard spectrum for a relevant ingredient of the bulk powder mixture by spectrophotometrically analysing characteristics of that relevant ingredient from transmission measurements of a beam of electromagnetic radiation applied to and passing through the relevant ingredient to provide a spectrum of absorption characteristics at known wavelengths of the beam;

removing a sample of powder from the bulk mixture and pressing powder of the sample into a self-supporting test wafer;

spectrophotometrically analysing characteristics of the material of the test wafer from transmission measurements of the beam of electromagnetic radiation applied to and passing through the wafer to provide an assay test spectrum of actual absorption characteristics of ingredients in the material of the test wafer for known wavelengths of the beam, and

comparing absorption characteristics from said assay standard spectrum with said assay test spectrum at predetermined wavelengths of the beam to assess acceptability of the relevant ingredient in the powder of the sample.

2. A method as claimed in Claim 1 and comprising pressing the powder of the sample into a wafer having

substantially flat and parallel opposed end faces through which said beam is directed.

3. A method as claimed in Claim 2 which comprises pressing the wafer as a cylinder with opposed flat and parallel end faces of the cylinder lying in radially extending planes perpendicular to the axis of the cylinder.

4. A method as claimed in Claim 3 in which the cylindrical wafer has a diameter in the range of 0.8 to 2.5 cm.

5. A method as claimed in any one of the preceding claims in which the bulk powder mixture is to be processed into predetermined dose weights by tableting or encapsulation and which comprises forming said wafer from sample powder having a weight in the range substantially corresponding to 0.5 to 1.5 said dose weight.

6. A method as claimed in Claim 5 in which said dose weight is in the range of 0.2 to 1.0 grams, preferably 0.25 grams.

7. A method as claimed in any one of the preceding claims which comprises pressing powder of the sample to a pressure in the range of 175 to 246 kg per square centimetre, preferably 211 kg per square centimetre, to form the wafer.

8. A method as claimed in any one of the preceding claims in which the beam is derived from a probe tip and which comprises moving the probe tip into abutment with the

self-supporting wafer for transmission of the beam through the wafer.

9. A method as claimed in any one of the preceding claims in which the beam transmitted through the wafer is directed through an aperture to detector means for measurement and which comprises locating the wafer to overlie the aperture with a peripheral marginal edge part of a flat end face of the wafer extending beyond the aperture and being in face to face abutment with a flat face of a wafer holder to alleviate stray light from passing between the wafer and the wafer holder to the detector means.

10. A method as claimed in any one of the preceding claims which comprises removing at least two samples of powder from spaced locations in the bulk mixture, pressing similar test wafers from the samples, providing assay test spectra for the respective test wafers and comparing absorption characteristics from said assay standard spectrum with said respective assay test spectra at predetermined wavelengths of the beam to assess acceptability of the distribution and/or concentration of the relevant ingredient throughout the bulk mixture.

11. A method as claimed in any one of the preceding claims which comprises predetermining at least two said assay standard spectra, one for each of a corresponding number of predetermined relevant ingredients in the bulk powder mixture, and comparing absorption characteristics from said respective assay standard spectra with said assay

test spectrum at predetermined wavelengths of the beam to assess acceptability of the respective relevant ingredients in the powder of the sample.

12. A method as claimed in any one of the preceding claims in which the or each relevant ingredient in the powder is an active ingredient or an excipient.

13. A method of analysing powder as claimed in Claim 1 and substantially as herein described.

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24

Application No: GB 9905318.3 **Examiner:** Rosie Hardy
Claims searched: 1-13 **Date of search:** 24 May 1999

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Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.Q): G1A (ACDX) (ACDL) (ADJS) G1B (BCX)

Int Cl (Ed.6): G01N 21/31 21/33 21/35 21/39 33/15

Other: WPI JAPIO EPODOC

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	GB 2328016 A PFIZER See pages 12 & 13	1, 12
X	GB 2292798 A MERCK & CO See pages 3 to 6	1, 12
X	US 5463223 MAG. K. WONG See cols. 3 to 5	1, 12

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